Infantile Diabetes

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Diabetes mellitus in infancy has been recognized since 1789 when Rollo reported the first authentic case. There have been subsequent reports through the nineteenth and twentieth centuries, but the condition is not common in the first year.

In a review made in 1934 at the Children's Memorial Hospital,[1] of 65 cases of diabetes occurring before the age of 13 years, only one patient was found to have had diabetes before the first birthday, while 11 patients had onset of the condition in the second year. By 1949, out of a total of 202 cases seen at this hospital there were 6 cases (3 per cent) in which diabetes developed in infancy.

Schwartzman, Crusius and Beirne[2] tabulated and reviewed 57 cases of infantile diabetes up to 1947. In this series the onset of diabetes occurred before the age of one year in 0.5 per cent. Joslin, Root, White, and Marble[3] reported seven cases occurring below the first year of life in a study of 1,430 diabetic children (0.5 per cent incidence) in agreement with the findings of the former group. John[4] recently reported two diabetic infants in a series of 500 patients with juvenile diabetes (or 0.4 per cent occurring in the first two decades of life).

Guest[5] reported a most interesting family of three consecutive siblings who were found to have diabetes

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under the age of one year, two at three months and one at nine days of age.

We are reporting the following cases to call attention to the clinical picture and the difficulties in making a correct diagnosis of diabetes mellitus in acutely sick children and to point out the important therapeutic measures. We feel that through the analysis of these case reports, an awareness of the possibility of diabetes will make for earlier diagnosis and treatment. In view of the high mortality, the need for earlier recognition is apparent. In our cases the correct diagnosis was made before admission in only one instance.

CASE REPORTS

Case 1. A ten-month-old baby boy was admitted to the Children's Memorial Hospital on January 27, 1927, with a history of vomiting and polyuria beginning two days before admission. Restlessness and labored respirations developed the next day. Examination revealed a comatose, pale, well-nourished infant with deep, rapid respirations, rales in the bases of both lungs and abdominal tenderness. There was an acetone odor to the breath. The temperature was 101° F. A diagnosis of ketosis was made. Glycosuria was discovered later; it was controlled with small doses of insulin.

After the fifth hospital day, he developed a severe diarrhea and vomiting, pneumonia and otitis media. He died on the twelfth hospital day of pneumonia, otitis media and acute intestinal intoxication.

Autopsy revealed gross atrophy of the pancreas, fatty changes in the liver and kidneys, broncho-pneumonia of the right upper lobe, emphysema and hypostatic edema and hyperemia of the lungs.

Case 2. A baby girl, aged 4¾ months, was admitted to the Children's Memorial Hospital September 18, 1942, with a history of vomiting and polyuria for three days. Rapid respiration and fever were noted the day of admission. In three days there was a weight loss of 2½ pounds.

Examination revealed a dehydrated infant with rapid respirations and acetone breath. She responded to stimuli. The chest was clear. The liver was enlarged. The temperature was 102° F. A diagnosis of renal anomaly and acidosis was made.

Later, the urine revealed sugar graded 4 plus, acetone, and diacetic acid. Blood sugar was 875 mg. per 100 cc. Non-protein nitrogen was 57 mgm. per cent and the carbon dioxide combining power was 10 volumes per cent. The leucocyte count was 36,000.

The treatment included the use of 700 cc. of one-sixth molar solution of sodium lactate, 300 cc. of saline solution with 5 per cent glucose and 44 units insulin. The sugar in the urine remained 4 plus, although the test for acetone became negative. The blood sugar fell to 420. The patient became less responsive. The temperature rose to 106° F., and she died seventeen and one-half hours following admission.

Autopsy revealed mild congestion of the bases of both lungs, fatty infiltration of the liver and a small pancreas. Microscopic study of the pancreas revealed pleomorphism of the islets with shrunken cells and pyknotic nuclei.

Case 3. A seven-month-old baby boy was admitted to the Children's Memorial Hospital December 12, 1943. The birth weight was 3½ pounds. A sibling, six years of age, had diabetes. The day before admission, he became restless and developed a high fever (104° F.) and abdominal distention. Initial physical examination revealed a dehydrated, acutely ill child. The eyeballs were rolled upward. The skin was dry. The anterior fontanelle was depressed, the respirations were rapid and there was an acetone odor to the breath. Dullness was elicited over the base of the right lung together with showers of fine rales at both bases. A diagnosis of broncho-pneumonia was made. Later, the blood sugar was 434; the test for carbon dioxide combining power was 20 volumes per cent. The urine contained sugar graded 4 plus; acetone was negative.

The treatment included 30 units of regular insulin; 400 cc. of one-sixth molar solution of sodium lactate; 600 cc. of saline solution containing glucose, followed hours.

The respiration became irregular and shallow and the infant was placed in an oxygen tent. The fever increased from 104° to 105° F. The respiration became very slow and coma developed. Later, gasping respirations were followed by long periods of apnea. The blood sugar twenty hours after admission was 105, the nonprotein nitrogen was 42 and the carbon dioxide combining power was 26 volumes per cent. Two and one-half hours later the respirations increased to 60 per minute and the baby was again gasping. His color became poor and he expired about twenty-four hours after admission.

Autopsy revealed a hemorrhagic broncho-pneumonia and a cloudy swelling of the liver. Microscopic examination of the pancreas with Goodpasture's stain revealed a normal number of islets. An abundance of

eosinophilic alpha cells were present. Occasional beta cells were identified.

Case 4. A baby girl, aged 11½ months, entered the Children's Memorial Hospital March 7, 1946, with a history of frequency of urination, fussiness, failure to gain and slight drowsiness for one month. Coryza and blepharitis were noticed six days before admission. Because of her failure to gain weight, a urinalysis was made; it revealed sugar, graded 4 plus. The birth weight was nine pounds, eight ounces. The father was six feet, eight inches tall.

The initial physical examination revealed a severely ill baby of good development and nutrition but with poor tissue turgor. The infant was restless. The respirations were 30 per minute and of the Kussmaul type. Acetone was present on the breath. The lungs were clear. The throat was mildly infected. The blood sugar was 288.

Treatment with insulin and fluids was followed by return of respiration to normal. Ketone bodies disappeared 18 hours after admission. Because of the fever of 101° F., penicillin was prescribed. Recovery was essentially uneventful. The patient was discharged from the hospital on a weighed diet and six units of protamine zinc insulin, with four units regular insulin in the morning and two units of regular insulin at night.

On November 30, 1949, she was 42 inches tall and weighed 44 pounds. The daily dosage of insulin then was one dose of 18 units of a mixture containing regular and protamine zinc insulin in a ratio of 2:1.

Case 5. A baby girl, 10 months old, was admitted to the Municipal Contagious Disease Hospital of Chicago December 15, 1948, with a history of croup for two days associated with anorexia and fever. Penicillin had been given orally for two days. Respiration became rapid and she vomited once. She had been brought to the hospital with a suspicion of meningitis.

The physical examination revealed a febrile infant with respirations of 48 per minute which were deep and grunting along with a flaring of the alae nasi. The temperature was 103° F.; the pulse rate was 160. Dullness was noted over the lower chest on the right but no rales were heard. The examination of the spinal fluid did not show cells or organisms; the tests for protein and sugar were normal. A specimen of urine, obtained the morning following admission, contained sugar graded 3 plus, but she was receiving glucose solution intravenously at the time. She was treated with chemotherapeutic agents for pneumonia and responded after the first twenty-four hours. On the third hospital day she was lethargic and the breathing was still labored in spite of treatment. Fluids were discontinued. The blood sugar was subsequently found to be 500. and the urinary acetone and diacetic acid were both graded 4 plus. Another specimen of urine, obtained four hours later, still contained sugar graded 4 plus.

Twenty units of regular insulin were given subcutaneously and, in three hours, 15 units more were administered. 500 cc. of one-sixth molar solution of sodium lactate was administered intravenously. Within 12 hours the infant responded to stimuli and the respiration was essentially normal in rate and depth. Orange juice and a weak formula were offered and were accepted readily. On the eighth hospital day, the child was transferred to the Children's Memorial Hospital. At this time the blood sugar was 362; the hemoglobin was 10 gm.; the red blood cell count was 4,260,000, the white cell count 7,800 per cu. mm. A six hour feeding schedule was established. Feedings consisted of whole boiled milk, vegetable, cereal and fruit. She remained afebrile and alert and was discharged on the thirteenth hospital day. Four units regular insulin twice daily and 6 units globin insulin once daily have controlled the glycosuria. There have been no subsequent complications.

Case 6. A baby boy, aged 12 months, was admitted to the Children's Memorial Hospital February 4, 1949, with a history of restlessness, anorexia for three days and a fever of 101° F. The day prior to admission he vomited twice and his respiration became heavy and rapid. The following morning, after vomiting twice, he was rushed to the hospital.

The physical examination revealed a well-developed comatose infant boy in shock and not responding to stimuli. The temperature was 103° F. rectally, and the respiration was 42 per minute, deep and regular; there was flaring of the alae nasi. The pulse, thready and weak in quality, was 136 per minute. Fine rales were heard at both lung bases with suppression of the breath sounds at the right base. Bronchial breathing was heard in the left axilla.

He was treated for pneumonia immediately with penicillin. Plasma and 250 cc. of one-sixth molar solution of sodium lactate were given intravenously. Supportive measures initially produced a good response. Within six hours after admission the chest had cleared remarkably with only a few rales remaining; however, the respiration remained deep and rapid and the patient was still comatose. A urinalysis revealed sugar graded 4

plus, acetone and diacetic acid. The carbon dioxide combining power of the plasma was 15.5 volumes per cent. The plasma chloride was 373 mg. per 100 cc. Twenty units of regular insulin were given subcutaneously. The same dose was repeated in three hours. After six hours, ten units were administered. At that time the urine showed sugar graded 2 plus, acetone and diacetic acid graded 4 plus. A total of 300 cc. of normal saline solution followed by 400 cc. of 5 per cent solution of dextrose in water were given intravenously.

Fifteen hours following admission the urine showed sugar 3 plus, and acetone and diacetic acid 4 plus. Ten units of regular insulin were then given. Response was noted shortly and the patient awakened. The sugar urine was only 1 plus, with acetone and diacetic acid 3 plus. Four units of regular insulin were given three hours after the last injection. Three hours later, 21 hours after admission, the patient developed severe, near fatal, insulin shock with apnea and cyanosis. He was revived by artificial respiration and rapid intravenous injection of a 10 per cent solution of dextrose in water. He was then placed upon a six hour management with intravenous feedings until he was able to eat, which was on the fourth hospital day.

On the seventh hospital day he developed a mild upper respiratory infection with a slight elevation of temperature. The insulin requirement rose from 4 units in twenty-four hours to 18 units in twenty-four hours. He was discharged alert and active on the twenty-first hospital day. Three doses of crystalline insulin per day have controlled the glycosuria. There have been no subsequent complications.

COMMENT

The age of onset of the disease in these six cases was 4½ months, 7, 10, 10¼, 10½, and 12 months. A family history of diabetes was recorded in two cases—one patient having a sibling with diabetes, the other a paternal uncle. The father of one child approached gigantism (*Case 4*). Four of these patients were of German extraction.

The pathological findings in *Case 1* revealed a gross atrophy of the pancreas, in *Case 2*, pleomorphism of the islets of Langerhans with shrunken cells and pyknotic nuclei, and in *Case 3*, a normal number of islets without apparent reduction of eosinophilic alpha cells but only an occasional beta cell.

The initial symptoms presented by diabetic infants are listed below in the order of frequency:

Fever, 100%
Pulmonary signs and symptoms, 100%
Accelerated respiration, 100%
Rales and signs of pneumonia, 66%
Anorexia and vomiting, 66%
Restlessness, 66%
Polyuria, 66%
Loss of weight, 33%

The susceptibility of infants with diabetes to severe respiratory infections leads to the predominance of fever and pulmonary signs and symptoms. This has not been recognized adequately in the past. Therefore, we wish to emphasize the need for consideration of diabetes when such symptoms are present. Special attention should be given when respiratory symptoms and signs improve or subside after the use of antibiotics and replacement fluid therapy but when hyperpnea and coma persist.[6] Early urinalysis and blood sugar determinations should be performed to establish an early diagnosis.

The administration of penicillin accelerated recovery in *Case 4* and probably prevented death in *Cases 5* and *6*. It is possible that all three patients who expired might have recovered from the diabetic acidosis and infection had penicillin been available to supplement insulin.

Adequate insulin therapy must always be prescribed. Severe hypoglycemia must be prevented. In *Case 6* insulin shock was almost fatal. It is probable that hypoglycemic shock caused death in *Case 3*, since the last blood sugar of 105 was recorded two and one-half hours before death and two hours before apnea was noted.

SUMMARY

Six cases of infantile diabetes are reported. In all cases, severe respiratory infections complicating diabetes dominated the clinical picture.

Attention is directed to the prominence of respiratory signs and symptoms. Penicillin therapy has favorably influenced the prognosis in infantile diabetes.

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DISCUSSION

ROBERT L. JACKSON, M.D. (*Iowa City, Iowa*): Recognized diabetes mellitus in infants is rare. In the past 26 years, 492 diabetic children with onset under 16 years of age have been observed in our clinic. Of these, 5 had onset during infancy (one per cent) and 24 had onset of their disease between the first and second year of life, making 5.8 per cent with onset under two years of age.

Of the 5 children with onset under one year of age, all responded satisfactorily to treatment; 3 have maintained a fair to good level of control, (as defined by us in our publication) for as long as 19 years and are living and well; one has maintained fair to poor control and has had frequent insulin reactions with possible central nervous system damage; the other patient was observed for 3 years, but her present status is unknown.

Of the 24 children with onset between the first and second year of life, 7 have maintained a good to excellent level of control for as long as 27 years and all are living and free from degenerative changes; 12 have maintained a fair level of control for as long as 25 years and are living, some have early signs of degenerative changes; the remaining 5 patients have maintained a fair level of control, one died, two have had central nervous system damage, and the exact state of the other two is unknown.

Anorexia, vomiting and diarrhea are very common symptoms of sick infants. The most common causes of illness in infants are infections of the respiratory and gastrointestinal systems. Inadequate intake or excessive loss of water, electrolyte and other nutrients deplete the infant's stores more rapidly than the older child or adult. Consequently, dehydration, ketosis and acidosis are frequently encountered in the nondiabetic infant. Urine specimens are more difficult to obtain from infants because of lack of bladder control and difficulty of collecting specimens, especially in baby girls. Therefore, routine urine examinations frequently are not done. The onset of diabetes mellitus in infants and young children is relatively abrupt because of the severity of the disease. Diabetes symptoms may not be elicited as a detailed history too frequenty is not taken; the symptoms of an infection may overshadow those of diabetes. It is easy to understand why the existence of diabetes mellitus, when it does occur in infants, may be overlooked.

The diagnosis is simple, providing the physician considers the possibility, and examines the urine and blood for sugar content. There may be suspicion of a small amount of sugar in the urine because of a false positive Benedict's test, from the relatively high content of reducing substance such as creatine and uric acid. However, a strongly positive reduction test always is found in infants and children with untreated diabetes. When the urine causes a mild reduction, the test should be repeated and the cause of the positive test should be found. Galactosuria in infants, in our experience, is much more common than glycosuria. Infants with definite galactosemia and galactosuria do not thrive and have an enlarged liver and a high incidence of cataracts. This inborn error of metabolism easily is treated by eliminating lactose in the diet. The diagnosis also is easy if the condition is thought of and laboratory procedures are done to identify the nonfermentable sugar. Seventeen infants with this condition have been observed in our clinic in the last 16 years as compared to only 5 infants with diabetes.

During acidosis and ketosis relatively large amounts of insulin will be needed to control diabetes, but, with improvement, the maintenance dosage will decrease rapidly to as little as three or four units a day. In measuring small doses for infants and younger children, we have found it desirable to employ a tuberculin syringe which will permit varying the dose by 0.4 units when using U 40 insulin or 0.2 units when using U 20 insulin.

Because of the lability of these very young patients and the decreased reliability of reduction tests of their urine (because of other reducing substances such as creatine), great care must be taken to avoid overdosage with insulin. There is the ever-present danger of irreparable damage to the central nervous system.

Growth and Development of Children With Diabetes Mellitus

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Growth and development are manifestations of life in the young and the rate and quality are related importantly to the general health and welfare of the child. For simplification I shall subdivide growth and development into five separate categories and attempt to make pertinent statements regarding each.

PHYSICAL GROWTH AND DEVELOPMENT

Numerous growth studies of children with diabetes mellitus have been reported.[1-7] These studies reveal that normal growth is compatible with controlled diabetes, but that there are many children with the disease who do not grow normally. The differences in the findings on the status of the height of the child at onset of diabetes by several authors may be accounted for in a large measure by the differences in the appropriateness of the standard used in evaluating the groups and by difference in the opinion of the several authors as to what constitutes a tall or a short child. The importance of an adequate diet has been established for the diabetic as well as the nondiabetic child. The importance of the level of control of the disease has not been given sufficient emphasis in most of the studies and too frequently, when degree of control is considered, objective criteria for establishing degree of control are not given.

In 1946 the records of 120 juvenile diabetic patients in our clinic were reviewed to determine the relationship between the growth of children with diabetes mellitus and the level of control of the disease.[8] The interpretation of the varying degrees of diabetic control is tabulated as follows:

Very Good to Excellent: Urine specimens are free from sugar except for very occasional traces; very occasional mild insulin reactions.

Good: Urine specimens are free from sugar except for occasional minimal glycosuria; occasional mild insulin reactions.

Fair to Good: More than one-half of the urine specimens free from sugar but minimal glyosuria in remaining specimens; occasional insulin reactions of varying degree.

Fair: Less than one-half of the urine specimens free from sugar and varying amounts of sugar in remaining specimens; occasional insulin reactions of varying degree.

Poor: Urine specimens contain varying amounts of sugar continuously; occasional insulin reactions.

Since growth in height of the normal child is more predictable during childhood than during pre-puberty and puberty, we studied the growth curves of 54 of the 120 diabetic children who had height observations two or more years prior to ten years of age. The differences in growth of these children, grouped according to level of diabetic control, were statistically significant.

Erratic growth was observed frequently in children with fluctuating degrees of diabetic control.

Growth observations were made on 93 diabetic patients after ten years of age. Despite the difficulty in evaluation and the unpredictable character of growth at this period there appeared to be a consistent tendency for growth to be normal or accelerated for the better

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degrees of control, and to be normal or less than expected with fair or poor diabetic control. In this group of older children there were eleven patients who were admitted to our clinic two to nine years after onset of the disease, and during the intervening time they had been in fair to poor diabetic control. Four of these patients accelerated after coming under our regimen of therapy even under fair diabetic control.

TABLE 1. Growth in Height Before 10 Years of Age Compared with that of Average Iowa City Children

Level of control of Diabetes Mellitus	Less		Erratic		Normal		Accelerated		Total
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number
Poor	3	38	1	12	3	38	1*	12	8
Fair	3	25	1	8	8	67			12
Fair to Good			3	19	10	62	3	19	16
Good	1†	8	1†	8	3	25	7	58	12
Very good to excellent					2	33	4	67	6
TOTAL	7	13	6	11	26	48	15	28	54

*This patient accelerated the first year of treatment when he was under fair to good diabetic control. He was emaciated at the time treatment was started and had been under poor diabetic control for more than one year.

†These patients failed to keep their appointments at the clinic, and their diets were not increased to satisfy their appetites.

A tendency was observed for the girls in the higher degrees of diabetic control to maturate normally and for those in the lower levels of control to have delayed maturation. A longer than average growing period was generally coexistent with delayed menarche.

With adequate management the diabetic children, on the whole, have maintained normal weight for their age and height and have gained normally during the years of observation included in this study. Twenty-six children showed a tendency to become obese, 21 during the ages 14 to 18 years. This was twice as common among adolescent girls as boys.

Normal growth does not preclude the development of degenerative changes, but when there is definite deceleration or stunting, degenerative changes develop earlier and progress more rapidly.[9]

EMOTIONAL GROWTH

The emotional pattern of a child and therefore of the adult becomes fairly well established during infancy and the early years of life, and it becomes progressively more difficult with increasing age, to alter this pattern. The emotional status of any patient with diabetes profoundly affects the regulation of his disease.[10, 11, 12] Unwholesome relationships between the child, his parents and others become exaggerated during adolescence. In my experience it is impossible to attain and sustain excellent control of the disease in an emotionally unstable patient. I am confident that few, if any, experienced diabeticians will take exception to this statement. The child with diabetes has, if anything, a greater need for security, affection and applause; he must learn to assume responsibilities commensurate with his age. Discipline is essential, and to be effective, punishment must be administered immediately after culpable acts of omission or commission, and of equal importance is forgiving or forgetting after the punishment has been given.

INTELLECTUAL DEVELOPMENT

The normal child who develops diabetes and is given good physical and emotional care will have normal intellectual growth.[4, 10] Frequent insulin reactions, and particularly severe insulin reactions, can and do cause irreparable damage to the central nervous system and must be avoided at any expense.

IMMUNOLOGICAL DEVELOPMENT

Gaining active immunity by immunization procedures or by having various types of infections is part of the growing-up process. It is well known that the physical condition of the child is related to his resistance to infection and the incidence of complications of infections. Children whose diabetes is well controlled are, in our experience, no more susceptible to infections than normal children and, providing proper adjustments are made during the time of infections, the degree of control need not be seriously altered. Children whose diabetes is not well controlled are not only more susceptible to infections than normal children, but more frequently develop complications from the infections as well as complications from loss of control of their diabetes. Chemotherapeutic and antibiotic agents have made it possible to combat more effectively intercurrent infections.

SPIRITUAL DEVELOPMENT

Although this phase of development tends to be overlooked in the secularism of our day, it should be a primary rather than a secondary consideration. The

home, the school and the church have serious responsibilities in this important area of growth. The child who learns to develop virtues rather than vices, has peace of mind and soul· can accept his disease and make unlimited contributions to his fellow men.

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Editing and the Editor

Medical writers, like all others, are not infrequently annoyed by changes made in their papers by the editors of the periodical in which the article is to be published.

Once a manuscript has been accepted, what then are the privileges and duties with respect to revision on the part of the editor and of the author? This is a difficult matter indeed and custom varies widely. Most of the popular magazines, once they have purchased an author's article, feel completely free to alter or rewrite it in any manner the editors see fit. At the opposite extreme are the editors of many medical and scientific journals who may publish an article, once accepted, word for word as submitted, in the obvious expectation that all faults and merits will be assigned to the author rather than to the journal.

This wide difference of practice indicates that there are no definite rules of the game. In my opinion, the editors of medical periodicals should take an intermediate position for papers believed by the editors to have merit but to require extensive changes. Before publication the manuscript should be returned to the author with suggestions by the editor given as specifically as possible, leaving any serious rewriting to the author. If this is done the authors should not be resentful, as is too often the case, but should realize that the editor is trying to assist him to prepare a more readable and better article. Even though the author may not agree with all the suggestions of the editor, he is usually wise to follow them, since the editor by reason of his profession is more likely to be familiar with the reaction of readers.

With manuscripts which are acceptable and which need only minor changes rather than extensive revisions, it is probably best for the editor or his assistants to make the necessary corrections and return to the author not only the proof but the original manuscript. In many of these cases, sentences or paragraphs which are not clear have been altered. Authors justifiably resent it when such editing changes the meaning. Therefore, the conscientious editor or manuscript editor would do well to call the attention of the author to any rewordings introduced which might possibly change the thought the author wished to convey.

Finally, the medical writers should not ordinarily object to the minor editorial revisions which are made by the editors of any periodical or book publishing house in order to bring the manuscript into conformity with the particular style adopted by the publisher. True, the author may not agree with the style adopted, but in submitting his manuscript he has tactily consented to abide by the rules of the periodical or publishers in question.

—From *Rx for Medical Writing*, by Edwin P. Jordan, M.D. and Willard C. Shepard, Philadelphia W. B. Saunders Company, 1952, page 33.

The Electroencephalogram of Patients with Diabetes Mellitus

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In 1946 Greenblatt, Murray and Root[1] reported a high incidence of "cerebral dysrhythmia" in diabetic patients with frequent severe insulin reactions ("problem" diabetics). Their findings have since been confirmed by the studies of Fabrykant and Pacella[2] and Wilson.[3] Greenblatt and others[1] found that 51 per cent of the 35 "problem" cases studied had abnormal electroencephalograms whereas, in a comparable control group of 40 patients with uncomplicated diabetes the incidence of abnormal EEGs was not increased over that in normal persons. Except for one patient in the control group, all were taking insulin. Long duration of diabetes did not appear to alter the incidence of "cerebral dysrhythmia". Administration of insulin over long periods of time had no apparent effect on the EEGs. Fabrykant and Pacella[2] also showed that the abnormalities were not due to the effect of the administered insulin. Six of the seven labile diabetics whom they studied had abnormal or borderline EEGs. Wilson[3] found eight cases of extremely labile diabetes in a series of 100 consecutive diabetic patients admitted to the hospital. Five of the eight cases had abnormal tracings. On the other hand, Strauss, Ostow, and Greenstein report a normal EEG in 23 cases of diabetes[4].

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In none of the reported studies have the criteria and type of EEG abnormality been clearly defined. No information is available in regard to the EEG and the level of blood sugar. Furthermore, the emphasis has been mainly on the "labile" or "problem" diabetic. For these reasons it was felt that a re-evaluation of the relationship of the EEG to diabetes would be in order. An attempt has been made to define more clearly the incidence, type, and distribution of electroencephalographic abnormalities in the general diabetic population and the influence of nine factors which might effect EEG.

METHOD OF STUDY

Patients. 81 patients with diabetes mellitus were used in this investigation. They were selected to obtain a wide range in age, duration of diabetes, insulin requirements, and stability of their carbohydrate metabolism. No patients with a personal or family history of convulsions prior to the onset of diabetes were included. All patients were ambulatory and they had not recently been in coma or insulin shock at the time of EEG study. They were classified into two main groups, the *relatively unstable group* (U) of 35 patients and the *relatively stable group* of 46 patients in accordance with criteria set forth in a previous paper.[5] The latter group was further subdivided into those receiving insulin (SC, 26 patients) and those controlled by diet alone (SS, 19 patients). Of those 19 patients, four had no symptoms of diabetes but did have mildly abnormal glucose tolerance tests. The mean ages and ranges of groups U, SC, and SS were 36.8 years (15-76), 58.9 years (25-76 years), and 54.6 years (22-75 years) respectively. While the three groups were comparable in age range, most of the young patients fell into group

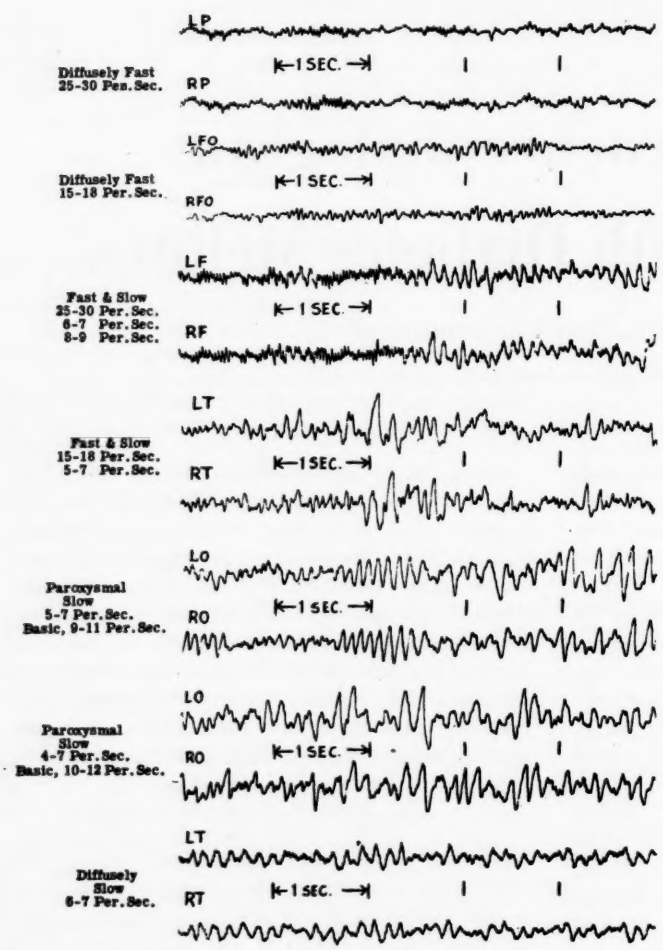

FIGURE 1 Examples of the different types of "abnormal" EEG's in the 81 patients studied.

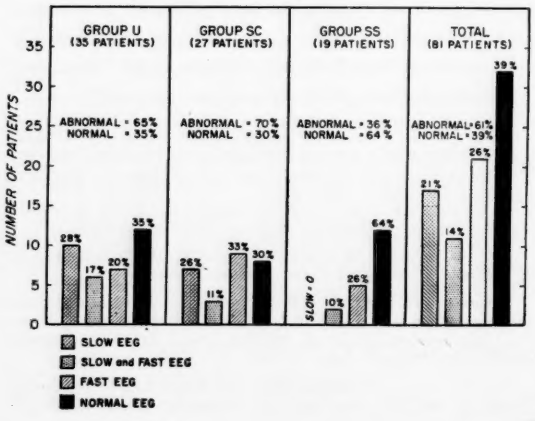

FIGURE 2 Incidence and type of "abnormal" EEG's among Group U (the relatively unstable group), Group SC (the relatively stable group receiving Insulin) and Group SS (the relatively stable group controlled by diet alone). For fuller explanation of group classification see text.

U. Groups U and SC were comparable in respect to amount and type of insulin used.

It should be emphasized that no sharp line of demarcation exists between stable or unstable patients or between those receiving and those not receiving insulin; nor can precise definitions be formulated. Nevertheless, the two major groups possess certain distinguishing features. The *relatively unstable group* is difficult to control; wide unpredictable swings in blood sugar levels are prone to occur unexpectedly with resultant waves of hypoglycemia and/or hyperglycemia and glycosuria; reactions to insulin tend to be frequent, severe, difficult to eliminate and aggravated by attempts to maintain normal blood sugar levels; ketosis develops rapidly. In

contrast, control is easy in the *relatively stable group;* fluctuations in blood sugar levels are decidedly less; reactions to insulin tend to be infrequent, explainable, and usually avoidable; ketosis is usually the result of gross neglect, infections, or both.

Neurological and Psychiatric Screening. Neurological examination was conducted on all patients to rule out the existence of organic disease of the central nervous system. In addition it was deemed advisable to screen all the patients used in the study by means of a mental status examination. This was limited to examination of the sensorium and included the following: 1) Orientation as to person, place and time. 2) Memory, recent and remote. 3) Retention. 4) Serial numbers repeated backward and forward. 5) Calculation. 6) Reading, writing, and speech. 7) Serial subtraction of 3 or 7 from 100. 8) Assessment of abstract thinking by use of proverbs, Kohs blocks and Goldstein stick procedures.

Electroencephalography. A Grass, 6 channel, model III C, electroencephalograph was used with 8 electrodes, routine placement, scalp-to-scalp and scalp-to-ear tracings. Twenty-two patients had one EEG, 53 patients had 2 EEGs from one to six months apart, and 6 patients had 3 EEGs. Repeat EEGs were different on only four occasions. Records containing more than random activity of slower than 8 per second or faster than 13 per second were regarded as "abnormal". Only fast activity of amplitude *greater than 20 microvolts* was classed as "abnormal". This follows the classification of Gibbs.[6] The significance of the so-called "abnormals" will be discussed later.

Blood Sugar Determination. Specimens of oxalated venous blood were obtained at the beginning and end of each EEG 137 times and analyzed for "true" blood sugar.

RESULTS

The following types of "abnormality" were noted in this series: 1) Bursts of high voltage slow activity, 2) Diffuse slowing, 3) Bursts of slow and fast activity, 4) More or less continuous fast activity of amplitude greater than 20 microvolts. Slow activity was bilateral, synchronous and not localized. Fast activity was more prominent in the anterior half of the brain and fell roughly into two ranges, 15-18 per second and 25-30 per second. Examples of each type of abnormality are illustrated in Figure 1.

The incidence and type of abnormal EEGs in the patients studied are summarized in Figure 2. In the total series 17 (21 per cent) had slow activity (S), 11 (14 per cent) had both fast and slow (FS), and 21 (26 per cent) had fast activity (F), a total of 61 per cent "abnormals". Among groups U and SC the incidence of "abnormals" was 65 per cent and 70 per cent respectively, while among SS it was 36 per cent with no S records. The 4 asymptomatic patients in group SS, noted above, had normal EEGs. The only statistically significant correlation between distribution of EEG type and classification of patients was in the lower incidence of slow activity (S and SF records) in the SS group as compared to that in the other groups ($P=.036$).

The incidence and type of EEG was analyzed statistically with respect to nine other variables which might conceivably be related to the EEG abnormality. The data were analvzed in two ways, the incidence of each type of EEG, (S, SF, F, and N), and the incidence of records with slow activity (S and SF) and records with fast activity (F and SF) against all others. Statistical analysis by the Chi square test yielded P values greater than 0.05, except in a few instances which will be mentioned below.

Blood sugar level at the time of the tracing. The lowest and highest blood sugars recorded were 32 and 602 mg. per 100 cc. respectively. Most of the blood sugar values fell between 100-300 mg. per 100 cc. Further, there were 14 patients whose blood sugar differed by more than 100 on repeat examination. No gross difference in the two EEGs was observed in any of these patients. On two occasions the blood sugar was less than 50 mg. per 100 cc., but was in the normal range when repeated; in neither instance was the EEG slow. Blood sugars were over 400 on 7 occasions, but no consistent trend as far as the type of EEG was observed. It is clear from these data that the EEG abnormalities cannot be accounted for on the basis of variations in the blood sugar level.

Age. The incidence of slow activity (S and SF) was greater in the younger age group (15-30) years and in the older age group (56-80), but this was not statistically significant. On the other hand, the fast activity (F and SF) was significantly more common in ages over 30, ($P=.038$). The rising incidence of fast activity with age will be discussed below.

Age at Onset of Diabetes. Records with slow activity (S and SF) were fairly well scattered among all the patients, but fast records tended to be more common among the patients whose diabetes began after the age of 30, that is, among the older patients, a correlation already noted.

Duration of Diabetes. There was no indication that the duration of diabetes influenced the type of EEG found among these patients.

Incidence of Coma or Acidosis. The patients were divided into three groups: 1) 19 with one or more episodes of coma or severe acidosis; 2) 13 who had had mild acidosis and ketonuria, but no coma; 3) 49 who had no recorded acidosis. No statistically significant differences were found as regards the distribution of EEG abnormalities in the three groups ($P>0.05$). Thus no evidence was obtained that any of the abnormalities resulted from the effects on the brain of previous acidosis or coma.

History of Insulin Reactions. (Table 1) There was a significantly greater incidence of records with slow activity (S and SF) among the patients who had had frequent insulin reactions in the past ($P=0.026$). In no instance had the patient had an insulin reaction immediately prior to the EEG. No other significant correlations were noted. We do not regard this as evidence that the insulin reactions are responsible for the slow activity because 15 patients with frequent severe insulin reactions had no slow activity in the EEG, while 8 patients with no insulin reactions did have slow EEG activity.

TABLE 1 EEG AND INCIDENCE OF INSULIN REACTIONS

EEG Type	Number of Patients with Frequent Reactions	Occasional Reactions	No Reactions
Slow (S)	10	4	3
Fast and Slow (FS)	5	1	5
Fast (F)	6	2	12
Normal (N)	9	4	20
Total	30	11	40

Presence of Retinopathy. Since retinopathy might mirror changes in the central nervous system, its incidence was compared with types of EEG. No significant correlation was found with slow activity, but fast activity was more common among patients with retinopathy ($P=0.013$). Since all but one of the patients with retinopathy was over 50 years in age, the greater incidence of fast activity may be accounted for on that basis.

Mental Status and Neurological Examination. No patient demonstrated any marked dementia, but eleven manifested minimal signs, including some concretization of thought; some recent memory disturbance; some decrease in span of attention, but without gross defects of memory, confabulation, disorientation, etc. Changes of this magnitude are frequently discovered among the older patients in this hospital when carefully examined. Seven of these 11 were over 70 years of age, the youngest was 53. Five had slow EEGs; one had mixed fast and slow; one had a fast record, and four had normal records. These data suggest that some of the slow activity in the older age group might be accounted for on the basis of organic brain disease, but this hardly explains the occurrence of slow activity in the 22 other patients who showed no evidence of dementia. Statistically there was no significantly greater incidence of records with slow activity among the patients with dementia. ($P=0.14$). Among the 11 patients with dementia the incidence of EEG abnormalities is about what has been reported in the literature.[7, 8, 9]

The neurological screening revealed the following:

One patient, a 24 year old woman with unstable diabetes, also had Friedreich's ataxia. She had no evidence of dementia. The EEG was classified as slow, but with no focal abnormalities.

Three patients had hemiparesis, presumably on a vascular basis. One had minimal dementia and a slow EEG, a second had no dementia and a slow EEG. The third patient, a 59 year old woman, suffered a left hemiplegia in 1935, with residual weakness still present in 1950. Her EEG showed fast activity on the left, frequency 15-20 per second, voltage 20-90 mv, and a dominant frequency of about 16 per second. On the right the doninant frequency 10 per second, with only small amounts of 16 per second activity. We classified this record as abnormally fast and considered the slower activity (actually within normal range) on the right as secondary to the earlier stroke.

One patient had the residuals of poliomyelitis contracted in infancy. She had no dementia. The EEG was classified as fast. There were six patients with peripheral neuropathy. Three had slow EEGs, one had a fast EEG, and 2 had normal EEGs. Three of the patients with abnormal EEGs also had dementia. One patient had a herniated nucleus pulposus and had a normal EEG.

One patient with a left-sided Bell's palsy had a normal EEG. A 23 year old woman with possible early multiple sclerosis had a normal EEG. A 33 year old woman had severe head trauma at age 16 but neurological examination in 1950 showed no abnormalities. EEG showed fast and slow activity, with no focal abnormalities. A 22 year old man had had a convulsion since the development of diabetes. His EEG was normal.

Thus careful neurological screening provided no evidence for neurological disease as an explanation for the EEG abnormalities.

Other Systemic Diseases. Since diabetics as a population show a high incidence of other systemic disorders, especially those related to vascular disease, we also analyzed our material from this point of view. None of these patients was delirious (although 11 had mild dementia as already discussed) so that EEG abnormalities could not be explained on such a basis.[10] There were 49 patients who had such complications and a number had more than one. In the series as a whole no significant correlation was found between EEG and the presence or absence of complications other than diabetes.

Twenty-seven patients had heart disease related to arteriosclerosis and/or hypertension. The distribution of EEG abnormalities was identical with that in the total group of 81 diabetics.

Nine patients had renal disease, including pyelonephritis and intercapillary glomerulosclerosis. Five had abnormal EEGs, including one S and four F. The one patient with the slow EEG had chronic azotemia, but no evidence of delirium.

Other complications included generalized and peripheral arteriosclerosis (without gross renal or cardiac disease), 7 cases; latent syphilis, 2 cases; pernicious anemia in remission, 2 cases; operated carcinoma of the breast, 4 cases; cirrhosis of the liver, 2 cases; asthma, 2 cases; mild hypothyroidism, 1 case. The small numbers did not permit any statistical evaluation.

COMMENTS

Our findings confirm the observations of previous investigators reporting the occurrence of abnormal electroencephalograms among diabetic patients. In the total series of 81 patients, the incidence of records with slow activity (S and SF) was 35 per cent, a significant difference from the 10 per cent which is generally accepted as the incidence in the so-called "normal" population. The incidence of diabetics whose EEGs showed fast activity (F and SF) was 40 per cent.

There would be no disagreement among electroencephalographers as to the significance of the slow activity which we have classified as "abnormal." More controversial would be the interpretation of the fast activity. We have designated as "abnormal" fast only activity of greater than 13 cycles per second occupying the bulk of the record and having an amplitude greater than 20 microvolts. Gibbs[11] reports among 1,000 adult controls 6 per cent with slightly fast activity and less than one per cent with very fast activiy. (F_1 and F_2 respectively, according to Gibbs' nomenclature.) Gibbs is vague in defining the difference between F_1 and F_2; "F_1, slightly fast; moderate amount of activity faster than 12 per second; F_2, very fast; large amount of activity faster than 12 per second. The amount is considered in terms of amplitude and frequency of the fast activity; the percentage of time it is present and the number of leads in which it appears."[11] We would assume from his description that the records which we have classified as fast correspond more closely to his F_2 category. According to Gibbs the incidence of slightly fast (F_1) electroencephalograms increases with age, being 3 per cent at age 15-18 and reaching 25 per cent by age 70.[11] Among our patients, the incidence of fast activity (F and FS) as defined by us was 15 per cent in the age group 15-30 years; 46 per cent in the group from 31-55 years; and 49 per cent in the group above 55 years. Since most of our records probably fall in the F_2 classification, which Gibbs regards as abnormal at any age, the incidence of fast records would be significant according to Gibbs. Yet Strauss and others[4] would classify Gibbs' F_1 and F_2 as normal. Mundy-Castle[12] studied the incidence of beta rhythm (14-30 per second) in the EEGs of normal adults. He reported 6.6 per cent of 211 normal adults as having some beta activity of amplitude greater than 20 microvolts, with an incidence of 3.7 per cent among 161 young adults (mean age 22.4 years) and 16 per cent among 50 "normal seniles" (mean age 75.1 years) Walters [13] states "transient bursts of activity at 14-30 c/second are seen in many normal records . . ." but he gives no data as to incidence, amplitude or amount. Schwab considers fast activity abnormal if greater than 30 microvolts in amplitude.[14] Thus, although electroencephalographers in general are much less certain about the interpretation of fast records, the statistical data available on so-called normals indicates a much higher

incidence of fast records among diabetics than the general population. It exceeds the 26 per cent reported by Gibbs as the incidence among 730 adult epileptics.[6]

Greenblatt and others[1] found the incidence of abnormal EEGs to be high among "problem" diabetics but not to exceed the normal incidence among uncomplicated diabetics. No such clear-cut distinction was evident in our records. 45 per cent of the "unstable" (U) diabetics had records with abnormally slow activity (S and SF), while the incidence among the "stable" (SC and SS) group was 26 per cent. If we exclude from this last group the 4 patients who had transiently abnormal glucose tolerance curves but no symptoms (and who may not be diabetics), the incidence of slow activity would be 29 per cent. The difference in incidence between the two groups was not found to be significant on statistical analysis, nor was there any difference in the incidence of fast activity (F and SF), which was 37 per cent and 41 per cent respectively.

The meaning of these findings remains obscure. We find no support for the hypotheses that the abnormal EEG relates in any way to the severity or stability of the diabetes or that it is a consequence of complications of diabetes. The greater incidence of slow records among patients who had frequent insulin reactions cannot be regarded as evidence either that the insulin reactions caused the EEG abnormality or that the EEG abnormality rendered the individual more vulnerable to hypoglycemia, as others have suggested.[1, 2] A different type of experimental design is necessary to establish such conclusions. While many records do closely resemble those seen among epileptics, this hardly seems sufficient basis to relate the two disorders or to provide a rationale for the use of anticonvulsants.[2, 3] There is no reason to believe that the fast activity and the slow activity necessarily have the same significance. The slow activity did not correlate with the presence of delirium or dementia. In this regard there is some resemblance between the findings in diabetes and in Addison's disease, where there is also found a high incidence of paroxysmal and diffusely slow records unrelated to delirium.[10, 15, 16]

Fabrykant and Pacella[2] have suggested the possibility of a genetic or constitutional factor causing the EEG abnormalities. The inability to correlate the EEG with any of the variables mentioned has suggested to us a similar hypothesis. Further studies are planned to examine the possibility of a genetic determinant and/or of a metabolic defect.

SUMMARY

Electroencephalographic studies were performed on 81 patients with diabetes mellitus. Thirty-five patients belonged to the *relatively unstable group* and 46 patients to the *relatively stable group*. Of the latter, 26 patients were receiving insulin, while 19 were controlled by diet alone. Neurological and psychiatric screening examinations were performed on each patient. Blood sugar determinations were made at the beginning and end of each EEG 137 times.

The following types of "abnormality" were noted in this series: 1.) Bursts of high voltage slow activity; 2.) Diffuse slowing; 3.) Bursts of slow and fast activity; 4.) More or less continuous fast activity of amplitude greater than 20 microvolts. Slow activity was bilateral, synchronous and not localized. Fast activity was more prominent in the anterior half of the brain and fell roughly into two ranges, 15-18 per second and 25-30 per second.

In the total series 17 (21 per cent) had slow activity, 11 (14 per cent) had both fast and slow, and 21 (26 per cent) had fast activity, a total of 61 per cent "abnormals." There was no statistically significant difference in the distribution of EEG abnormalities in the 3 groups of diabetics except for a lesser incidence of slow activity among the stable diabetics not receiving insulin.

The incidence of slow activity was greater in the younger age group (15-30) years and in the older age group (56-80) but this was not statistically significant. Fast activity was significantly more common in ages over 30.

A significantly greater incidence of records with slow activity was noted among the patients who had had frequent insulin reactions in the past. However, 15 patients with frequent severe insulin reactions had no slow activity in their EEG records while 8 patients with no history of insulin reactions did have slow activity.

No significant correlations between EEG type and blood sugar, duration of diabetes, incidence of coma or acidosis, minimal dementia, or associated systemic or neurological disease could be made.

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DISCUSSION

DR. MAXIMILIAN FABRYKANT (*New York*): In a group of 16 labile diabetics studied with Drs. B. L. Pacella and J. H. Taterka, a normal electroencephalogram was obtained in only three. In the remaining 13 cases there was no uniformity in the recorded alterations of the EEG pattern. This is in agreement with data presented by Dr. Izzo and his associates. We were also unable to establish a definite correlation between the type and the degree of the disturbance in cerebral electroactivity and the degree of lability of diabetes, except for the fact that a marked distortion of the EEG was seen only in those who were subject to severe insulin reactions. Thus patterns consistent with convulsive tendency were recorded in six, and suggestive of focal brain pathology in three such patients.

While no sufficient information is available as yet to offer a satisfactory explanation for the development of EEG abnormalities in diabetes, some known facts seem to be significant in this connection. Inasmuch as we have obtained a disturbed brain wave pattern in non-diabetic blood relatives of several of our diabetic patients, we have previously suggested that the disordered cortical potentials may be genetic or constitutional in origin. Further studies revealed that EEG abnormalities may be found in apparent absence of a genetic factor in those who were repeatedly subjected to severe and prolonged insulin reactions.

True, there is no strict parallelism between the height of the blood sugar and the electroactivity of the brain. Critically low blood sugar values associated with normal EEG patterns were reported in various hypoglycemic states, including that due to pancreatic islet tumors. However, it is known that severe hypoglycemic episodes may produce injury to the brain. We therefore believe that some of the EEG abnormalities recorded in diabetic patients are genetic or constitutional in origin while others are secondary to repeated severe insulin reactions and reflect metabolic and functional disturbances of the brain cell resulting from severe hypoglycemia.

Dr. Izzo and his associates found no correlation between the frequency of insulin reactions and the alterations of the EEG. However, I find it significant that in their patients treated with diet alone the incidence of abnormal EEG tracings was only 36 per cent as against 65 per cent and 70 per cent in those who received insulin therapy. Thus their statistics do not necessarily support their view that the abnormal EEG is not in any way related to the severity of diabetes or to complications of this disease. Certainly, with regard to EEG abnormalities, the important point is not the frequency but rather the severity of insulin reactions.

Dr. Izzo and his associates find no rationale for the use of anti-convulsants in diabetes. To this I would take exception since it is recognized that anticonvulsants may be useful in certain nonepileptic conditions, and may even reduce the irritability and excitability in major psychoses. Our exceedingly satisfactory results with the use of anticonvulsive therapy in labile diabetes have been recently confirmed by D. R. Wilson (Canad. M. A. J. 65:462, 1951). Moreover, in our experience anticonvulsants may produce a marked improvement in the initially abnormal EEG patterns of labile diabetics.

The work of Dr. Izzo and his associates is of considerable interest. They have presented evidence that EEG alterations may be found in a surprisingly large proportion of diabetics, even in mild diabetics who received no insulin therapy. To my way of thinking, their work opens up new leads for a study of functional or structural brain changes which may be present in a great number of diabetic patients.

Steroid Diabetes In Man

THE DEVELOPMENT OF DIABETES DURING TREATMENT WITH CORTISONE AND CORTICOTROPIN

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Observations on the development of diabetes have been made in five cases in which corticotropin (ACTH) and/or cortisone were used for the treatment of the basic disease. A detailed analysis of the diabetes, observed with a follow up on its subsequent course lasting up to 1½ years, is presented. Special attention is devoted to a comparison of the features of the diabetes with those previously described as steroid diabetes in animals [1-4] and man.[5,6]

CLINICAL AND LABORATORY DATA

Case 1† W.E., a 51 year old white man, entered the hospital in November 1949 with a history of drenching night sweats, migratory arthralgia and left chest pain, pleuritic in character. A diagnosis of disseminated lupus erythematosus was established by the presence of fever, pleuritis, pericarditis, mild anemia, relative leucopenia, elevation of the sedimentation rate, hyperglobulinemia and Hargraves' cells in the buffy coat of the sternal marrow and peripheral blood. After an initial 15 day course of cortisone the patient was treated continuously, with but four brief interruptions, with corticotropin for over two years.

It is of interest that 3 members of this patient's family had diabetes. His mother developed diabetes in her late fifties, but did not require insulin to the time of her death, which occurred at the age of 64 from a cerebrovascular accident. A sister, weighing 335 pounds, was found to have diabetes nineteen years ago at the age of 35. She required insulin for one year during which time she lost 100 pounds in weight. Since then she no longer requires insulin and is said to have a normal blood sugar without glycosuria to the present time. A paternal second cousin developed diabetes in her late forties; it was controlled by diet until the time of her death from a stroke.

The patient had no clinical evidence of diabetes mellitus prior to hormonal treatment; two fasting blood sugar determinations were 80 and 87 mg. per 100 cc. and repeated examinations of the urine were negative for sugar. He received a 15 day course of cortisone intramuscularly (total dosage 1.85 gm.) without any clinical evidence of diabetes; the fasting blood sugar values were normal and the urine was sugar free. During this period the sodium content of the diet was restricted to 500 mg. without any carbohydrate restriction.

The patient was then started on a course of corticotropin: 75 mg. daily in divided doses. Within four days he developed polydipsia, polyuria, hyperglycemia and glycosuria. The fasting blood sugar was 230 mg. per 100 cc.; examination of the urine revealed glycosuria (graded 3 plus) without acetonuria. During the ensuing two weeks, despite a voracious appetite and marked improvement in his clinical condition, his weight continued to drop from 129½ to 120 pounds; the urinary output increased markedly, reaching a maximum of over 6500 cc. on one day. Despite a reduction of the dosage of corticotropin to 35 mg. per day, the level of glycosuria and hyperglycemia remained unchanged.

† This case was made available to us through the courtesy of Drs. George Baehr and Henry Horn, New York City.

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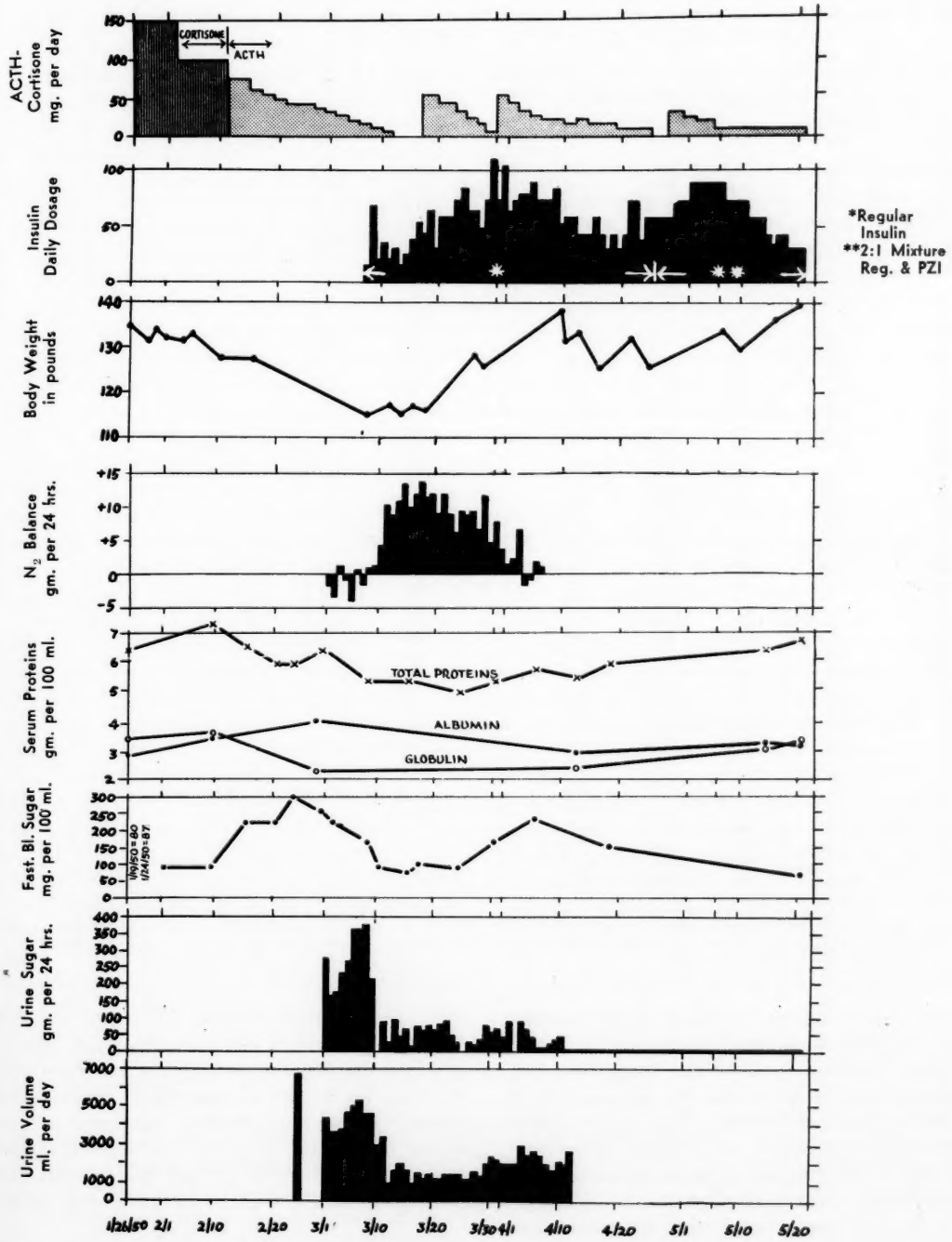

FIGURE 1 Case 1. Development of diabetes during corticotropin therapy. Pertinent clinical and laboratory data are presented.

TABLE 1 Case 1. Food intake, nitrogen balance, urinary volume and glucose, and fasting blood sugar levels during period of balance studies. For additional details see text and Figure 1.

		Diet		Urine					Therapy	
Date	Weight lbs.	Carbohydrate gm.	Nitrogen gm.	Volume ml.	Glucose gm.	Nitrogen gm.	Nitrogen Balance gm.	Fasting Blood Sugar mg.%	Corticotropin mgs.	Insulin Units Per Day
3/1/1950	120	200	24.2	3380	281	25.3	— 2.4		35	
2	119½	363	24.2	2730	175	24.0	— 3.1	238	30	
3	120	200	24.2	2745	176	21.6	+ 1.3		30	
4	119½	350	24.2	2800	179	23.6	— 0.7		25	
5	119½	350	24.2	3800	236	26.7	— 3.8		25	
6	119	350	24.2	4080	262	22.5	+ 0.4		20	
7	119	350	24.2	4420	366	24.6	— 1.7		20	
8	118½	350	24.2	3650	365	22.4	+ 0.5	180	15	
9	117¾	350	24.2	3740	374	21.4	+ 1.5		15	15
10	118	350	24.2	3760	218	18.2	+ 4.7	95	10	70
11	115½	350	24.2	2045	0	12.4	+10.5		10	20
12	115½	350	24.2	2400	91.2	14.0	+ 8.9		5	35
13	114½	350	24.2	1020	24.2	11.8	+11.1		5	20
14	116	350	24.2	1600	92.8	9.0	+13.9			30
15	117½	350	24.2	2000	48.4	12.8	+10.1	75		15
16	116½	350	24.2	1560	62.4	10.8				25
17	115½	350	24.2	995	17.7	8.7	+14.2	100	50	40
18	115	350	24.2	1420	76.6	11.3	+11.6		50	55
19	116½	350	24.2	1130	61.0	11.2	+11.7		50	45
20	118½	350	24.2	1510	78.5	13.6	+ 9.3		40	65
21	119½	338	24.2	1195	67.0	11.2	+11.7		40	30
22	119½	—	24.2	1740	87.0	13.5			40	60
23	122¾	350	24.2	1910	91.6	16.7	+ 6.2		30	60
24	123	350	24.2	1920	51.0	13.1	+ 9.8	90	30	100
25	—	350	24.2	1280	21.8	13.3	+ 9.6		20	75
26	—	350	24.2	1335	0	13.1	+ 9.8		20	85
27	125	350	24.2	1550	21.7	17.2	+ 6.7		15	65
28	127¾	350	24.2	1490	13.9	10.9	+12.0		10	65
29	125	350	24.2	2045	33.6	18.1	+ 4.8		10	50
30	126	300	24.2	2380	74.7	15.2	+ 7.8	180	50	75
31	126½	352	24.2	2120	5.4	21.6	+ 3.2		50	110
4/1/1950	127	350	24.2	2000	58.0	21.9	+ 1.0		40	75
2	128½	352	26.1	2135	44.6	22.9	+ 1.9		40	105
3	129	352	26.1	1995	91.8	18.6	+ 6.2		30	65
4	130	352	26.1	3160	89.1	26.5	— 1.7		30	75
5	131¾	352	26.1	2650	92.3	25.6	— 0.8		25	80
6	132	352	26.1	2780	64.0	22.8	+ 2.0	260	25	80
7	132	352	26.1	2470	49.4	23.4	+ 1.4		20	90
8	132½	352	26.1	2000	trace				20	75
9	132½	352	26.1	1630	trace				20	75
10	134½	350	24.0	2125	19.1				20	75
11	133½	350	24.0	2020	21.2				15	85

*Nitrogen balance figures were determined by calculation of the nitrogen intake of the weighed diet, analysis of the urinary nitrogen, and utilizing a figure of 1.3 gm. of nitrogen as the average fecal nitrogen excretion, as has been previously suggested.[20]

Eighteen days after the institution of corticotropin therapy, and fifteen days after the discovery of glycosuria, more intensive studies of the carbohydrate and protein metabolism were initiated. He was placed on a fixed diet with measured intake of 350 gm. of carbohydrate, 150 gm. of protein, and 100 gm. of fat after minor adjustments because of his ravenous appetite. Daily quantitative estimations of the urinary excretion of nitrogen and glucose were made (Figure 1 and Table 1)*.

For the first eight days of this period, the daily dosage of corticotropin was gradually reduced from 35 to 15 mg. per day; averaging 25 mg. per day. During this time his weight declined from 120 to 117¾ pounds. The polyuria continued, the output of urine varying from 2730 to 4420 cc. per day. The glycosuria ranged from 175 to 365 gm. per day. The nitrogen balance† ranged from minus 3.8 to plus 1.3 gm.

*We are indebted to Dr. Herbert Pollack in whose laboratory these determinations were performed.

†The difference between estimated nitrogen content of the food and the actual determination of the nitrogen excretion of the urine plus a constant figure of 1.3 gm. nitrogen as the avearge daily fecal nitrogen excretion.[20]

per day, averaging minus 1.2 gm.

The patient was then given regular insulin in divided doses, the dosage being determined by the degree of the glycosuria. The balance studies were continued for the next 30 days. The daily insulin dosage ranged from 15 to 110 units per day, averaging 60 units. During this period the dosage of corticotropin varied from 0 to 50 mg. per day, averaging 25 mg. per day.

Four days after institution of insulin therapy, his weight started to increase while the urine volume and glycosuria decreased. He gained 18 pounds in this 30 day period. The glucose excreted in the urine showed considerable fluctuation since strict control was never attempted, because it was felt that the glycosuria and hyperglycemia would spontaneously decrease with the reduction of the dosage of corticotropin, as was borne out by the later course. The nitrogen balance became markedly positive ranging from minus 1.7 to plus 14.2 gm. N per day, averaging plus 7.0 gm.

For the remainder of his hospital and supervised convalescent care (60 days), the patient continued to show marked clinical improvement though he did develop an episode of pneumonia which responded to antibiotic therapy. He continued to receive corticotropin reaching a constant maintenance dose of 10 mg. per day. For the last two months of this period he was on a mixture of protamin zinc and regular insulin. The urine showed intermittent glycosuria; it gradually disappeared as the dosage of corticotropin was reduced.

Since discharge, the patient has remained free of symptoms. For the past 18 months he has been maintained on a daily dosage of 5 to 10 mg. of corticotropin except for a 7 week period when he received no hormonal therapy. This dosage has successfully controlled the fever and arthralgia. He has had no symptoms of diabetes.

One year after discharge (June 1951) an oral glucose tolerance test was normal. Subsequent fasting blood sugars have been normal, and examination of casual urine specimens has revealed no glycosuria. He has gained 58 pounds since the glycosuria and hyperglycemia were first noted.

Comment A patient with disseminated lupus erythematosus was treated with a short course of cortisone, followed by 2 years of corticotropin therapy. He had a family history of diabetes. During the course of cortisone therapy, the blood sugar level remained normal and there was no glycosuria. Shortly after the initiation of corticotropin treatment, the patient developed glycosuria and hyperglycemia with an impairment of glucose tolerance characteristic of diabetes mellitus. Studies prior to the institution of insulin therapy revealed glycosuria, without acetonuria, increased urinary output, a negative nitrogen balance, and weight loss, despite the intake of 2900 calories with 150 gm. of protein daily.

Following the institution of insulin therapy there was a pronounced diminution of the urine volume and glycosuria, a gradual weight gain and a positive nitrogen balance. As the dosage of corticotropin was decreased the insulin required for control of the glycosuria diminished and it was finally discontinued. For over 1½ years the patient has remained aglycosuric without insulin therapy while on treatment with 5 to 10 mg. of corticotropin. A glucose tolerance test one year after the cessation of insulin therapy, while the patient was on small doses of corticotropin, revealed no impairment of carbohydrate tolerance.

*Case 2** J. W., a 40 year old white man, entered the hospital with a past history of right-sided pleuritis 23 years ago, empyema of the right pleural cavity 21 years ago, and generalized arthralgia 9 years ago. He noted a persistent dry cough for the last 3 years. In the last year, the cough became productive of mucopurulent sputum and was associated with exertional dypnea, wheezing respirations, a spiking recurrent nocturnal fever and an 18 pound weight loss. His family history was pertinent, in that two paternal uncles were known to have diabetes; one requiring insulin therapy.

A diagnosis of Boeck's sarcoid was made on the basis of history, the presence of splenomegaly, lymphadenopathy, the physical and roentgen findings of the chest, and the negative results of investigation for a bacterial, fungal or tuberculous infection. It was substantiated by a positive lymph node and endobronchial biopsy and by a positive Nickerson-Kveim test.

After a prolonged course of varied antibiotic therapy, without effect on the fever or respiratory symptoms, the patient was given a 62 day course of cortisone by intramuscular injection, totaling 7.975 gm. Prior to this treatment, the fasting blood sugar was 98 mg. per 100 cc. and repeated urine examinations were negative for glucose. His fasting blood sugar remained normal (85 and 115 mg. per 100 cc.) and the urine was sugar free. During this time, the patient was on a diet containing 200 mg. of sodium without any restriction of the carbohydrate intake. Definite improvement was marked

* The clinical features of this case have been previously reported.[9]

TABLE 2 Case 2. Body Weight, urine and blood sugar during courses of corticotropin therapy.

Date	Weight pounds	Urine Sugar	Blood Sugar mg. %	Treatment Cortisone mg. per day	Treatment Corticotropin mg. per day
3/3/51	185		98		
3/19					
4/7	182				
4/10,17,21					
4/24-4/25				25	
4/26	177¾			100	
4/27				100	
4/28				100	
4/29-30				100	
5/1				100	
5/2			85	100	
5/3				100	
5/4,5				100	
5/6,7				100	
5/8			115	100	
5/9,10	171			100	
5/11-6/21				150	
6/22	175½			100	
6/23				75	20
6/24				75	80
6/25				50	80
6/26	174¾				80
6/27,28					60
6/29,30					40
7/1-7/5					80
7/6					80
7/7					75
7/8					60
7/9			290		60
7/10			290[1]		
7/11		tr.tr.	195		60
7/12					40
7/13		4	225[2]		40
7/14		tr.0,0			40
7/15		0,tr.tr.			30
7/16		0,0,2			30
7/17,18					30
7/19-7/22					15
7/23	169¼		95		15
7/24-8/2					
8/3			110[3]		
8/4-8/5					
8/6			96[4]		
8/7					
8/8		tr,0			100
8/9		0,tr,0			100
8/10		0,0,0,0	165		100
8/11		0,tr,tr			80
8/12		0,tr,tr,tr			80
8/13		0,tr	156		80
8/14		0,0,0,tr			80
8/15					80
8/16		ft. tr	82[5]		80
8/17			140[6]		60
8/18	175½				40
8/19-9/13					0
9/14			76[7]		0

[1] Blood sugar determination done 2½ hours after breakfast.
[2] Fasting blood sugar of glucose tolerance test, Fig. 2 Curve A
[3] Fasting blood sugar of glucose tolerance test, Fig. 2 Curve B
[4] Fasting blood sugar of glucose tolerance test, Fig. 2 Curve E
[5] Fasting blood sugar of glucose tolerance test, Fig. 2 Curve C
[6] Fasting blood sugar of glucose tolerance test, Fig. 2 Curve F
[7] Fasting blood sugar of glucose tolerance test, Fig. 2 Curve D

by a lowering of the fever, reduction of the cough and sputum production and improvement of the roentgenologic and bronchoscopic findings.

Two days before cortisone therapy was stopped, corticotropin administration was started. It was given intramuscularly every 6 hours in daily doses, ranging from 80 to 15 mg. for a period of 30 days. The total dosage of corticotropin was 1.57 gm. On the eighteenth day of this therapy, while on a daily dose of 60 mg., he was found to have fasting hyperglycemia (blood sugar 195), and mild glycosuria without acetonuria. Two days later, an oral glucose tolerance test revealed a diabetic type curve (Figure 2, Curve A). Glycosuria ranged from 1 to 4 plus and disappeared after 6 days as the dosage of corticotropin was gradually lowered to 15

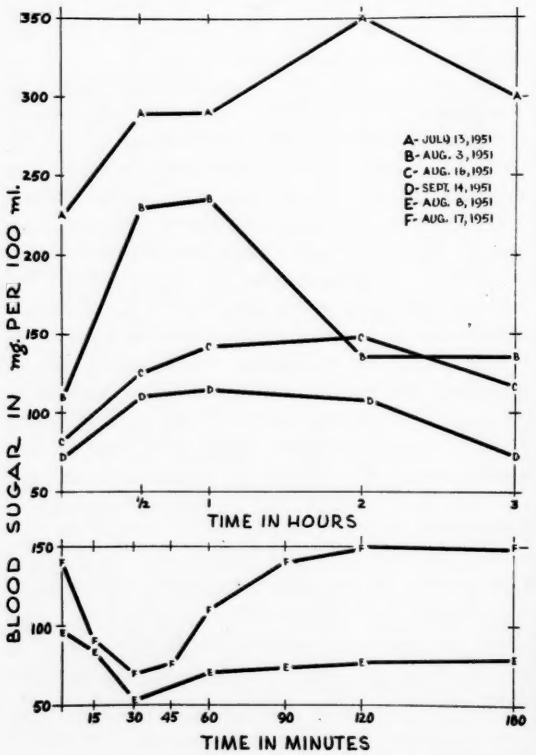

FIGURE 2 Case 2. Curves A to D. Glucose tolerance tests during, between, and after courses of corticotropin therapy (100 gm., orally).

Curves E and F. Insulin tolerance tests before and during the second corticotropin course (10 units regular insulin, intravenously).

mg. daily (Table 2). During this period, the patient lost 5 pounds despite a lower fever and a good appetite and food intake.

Ten days after the cessation of corticotropin therapy a repeated oral glucose tolerance test revealed a curve considered to be at the upper limits of normal (Figure 2, Curve B). An insulin tolerance test was normal (Figure 2, Curve E).

The patient was then placed on a 10 day course of corticotropin in doses ranging from 100 to 60 mg. per day. Again, hyperglycemia and a mild glycosuria were noted. The fasting blood sugar rose from the pretreatment levels of 96 and 100 mg. per 100 cc. to 165, 156, and 140. The glucose tolerance test showed a prolonged plateau and was mildly diabetic on the ninth day of treatment while the patient was receiving daily 80 mg. of corticotropin (Figure 2, Curve C). An insulin tolerance test showed a higher initial level and a more rapid return to the original level than the previously performed test, which may be interpreted as a slightly impaired response (Figure 2, Curve F). Again, the patient lost 6 pounds during the ten days of treatment.

One month after the cessation of corticotropin treatment, an oral glucose tolerance test was repeated and was found to be normal (Figure 2, Curve D).

Comment A 40 year old white man with proven Boeck's sarcoid was treated with cortisone for 62 days and corticotropin for 30 days. The patient had a family history of diabetes mellitus. During cortisone therapy there was no evidence of impaired carbohydrate metabolism. While on corticotropin, he developed hyperglycemia, glycosuria and the glucose tolerance test proved to be diabetic. Ten days after stopping corticotropin, glucose and insulin tolerance tests were normal.

During a second 10 day course of corticotropin, he again developed glycosuria and impairment of glucose and insulin tolerance. During both periods of corticotropin therapy he lost weight despite a good food intake, perhaps indicative of a negative nitrogen balance. At no time did he develop acetonuria. One month after the course of corticotropin therapy he had a normal glucose tolerance test.

Case 3 E. M., a 60 year old white male, entered the hospital in May 1950 with a 10 year history of progressively disabling rheumatoid arthritis involving the joints of all the extremities and the vertebral column. He had received multiple courses of salicylates, gold, antibiotics and physiotherapy during the course of his illness. At the time of admission, he was completely immobilized due to his joint deformities and atrophy of his musculature. He weighed 95 pounds. He was given a course of intramuscular cortisone therapy totaling 1.875 gm. over a period of 13 days. (Table 3). There was some subjective relief, but no fall in the sedimentation rate or increase in the range of joint motion.

Ten years prior to admission a casual urine specimen is said to have shown glucose, but a repeat examination was negative for reducing substances. There was no family history of diabetes.

On admission, the fasting blood sugar was 95 and no glycosuria was present. Two days after the initiation of cortisone therapy in doses of 150 mg. daily, the fasting blood sugar was 210. Subsequent determinations during the course of cortisone therapy were 190 and 185. Glycosuria was present in quantities ranging from 30 to 60 gm. per 24 hours, after the cessation of cortisone therapy. Two weeks after the cessation of cortisone therapy, protamine zinc insulin was given, 25 units daily. The urine became sugar free in 24 hours. Insulin in decreasing dosages was given for 5 days with complete cessation of glycosuria.

Periodic urine examinations over a period of 6 weeks after discharge were negative for glucose. At the end of this period, the patient was given a 60 day course of cortisone, in doses of 100 to 200 mg. daily by his private physician. Again a 3 to 4 plus glycosuria was noted within a few days after the onset of therapy. The glycosuria persisted throughout the course of cortisone therapy but disappeared shortly after the cessation of treatment.

Fifteen months after his hospitalization (August 1951) this patient showed no essential change in his clinical status. His urine had remained free of glucose. However, an oral glucose tolerance test with 100 gm. of glucose was diabetic in character. Though the fasting blood sugar was normal, there was a progressive rise from 72 to 200 mg. per 100 cc. at the third hour (Table 3, Footnote 3).

Comment This patient had a long-standing, crippling, rheumatoid arthritis with a questionable glycosuria at one examination ten years prior to the institution of cortisone therapy. There was no family history of diabetes. Diabetes immediately followed the use of cortisone. Very shortly after the cessation of treatment fasting blood sugars and urine examination for glucose were normal. A second course of cortisone treatment again resulted in glycosuria which promptly disap-

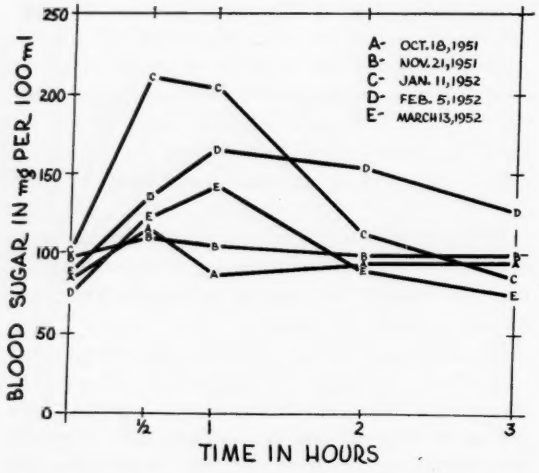

FIGURE 3 Case 4. Glucose tolerance tests before and during a prolonged course of corticotropin therapy in a patient with non-tropical sprue.

Note the flat glucose tolerance tests prior to therapy (A and B) characteristic of sprue; diabetic glucose tolerance tests during therapy (C and D) with return to normal on low maintenance doses (E).

TABLE 3 Case 3. Urine and blood sugar values during and after a course of cortisone therapy.

Date	Urine Glucose gm.%	Blood Sugar mg.%	Treatment: Cortisone mg. Per Day	Treatment: Insulin-PZI Units Per Day
5/17/50	0	95	—	
5/22-23/50			150	
5/24/50			150	
5/25-5/31/50			150	
6/1/50	trace to 3+		150	
6/2/50	1.7		150	
6/3/50	3.3	190	75	
6/5/50	3.9			
6/6/50	2.5			
6/7/50	5.0			
6/8/50	4.0			
6/9/50	2.5	185		
6/12/50	2.5			
6/13/50	2.0			
6/14/50	3.3			
6/15/50	3.3			
6/16/50	3.3			
6/17/50	1.0			25
6/18/50	0			25
6/19/50-6/21/50	0			15
6/22/50	0			
6/23/50-8/?/50	0			
8/50-10/50	2-4+		200[1]	
10/50-8/8/51	0		100[2]	
8/9/51	0	72[3]		

[1] Daily dosage for 15 days.
[2] Daily dosage for 45 days.
[3] Oral Glucose Tolerance Test

	F	½	1	2	3 hrs.
Blood	72	88	119	162	200
Urine	0	0	¼%	¼%	¼%

peared with the cessation of therapy. An oral glucose tolerance test 15 months after the first course of cortisone therapy showed a normal fasting value, but was diabetic in character. The presumption was that this patient may have had an impaired glucose tolerance prior to cortisone therapy.

Case 4 C. H., a 43 year old white woman, was admitted to the hospital in September 1951 with a history of crampy abdominal pains, frequent frothy, foul smelling stools without blood or mucous, and a 30 pound weight loss over a two year period. Diagnostic work-up, at the Consultation Service of this hospital in February 1951, had suggested the diagnosis of a sprue syndrome on the basis of type of the diarrhea and evidence of a "deficiency pattern" of the small bowel on roentgen examination.

From February 1951 to the time of her admission in September, she was treated with multiple injections of vitamins, including folic acid, vitamin B^{12}, and liver extract without change in her condition. In July, she received a 10 day course of cortisone intramuscularly with minimal symptomatic relief. In September, at another hospital, laparotomy was performed and an edematous small and large bowel was noted. A lymph node removed at that time revealed a hyperplastic lymphadenitis, and a liver biopsy showed early fatty infiltration.

Her family history is significant in that her father died of diabetes mellitus. Upon admission, the prominent signs and symptoms were the evidence of marked weight loss and malnutrition, diarrhea, moderate anemia and marked asthenia. The stools were light in color and contained large quantities of undigested fat, the total fat content being 60.5 per cent of dry fecal weight. A gastrointestinal roentgen study showed a rapid transit time and a pattern suggestive of sprue. The oral glucose tolerance test was flat, (Figure 3, Curve A). A vitamin A tolerance test showed extremely low serum levels and no absorption; the fasting, 4, 6 and 8 hour levels being 14, 12, 12, and 10 micograms per 100 cc. respectively. The serum carotene level was extremely low, 7 micograms per 100 cc.

For a period of 10 weeks treatment included vitamins, liver injections, folic acid, vitamin B^{12}, Sorbitan,

pancreatin in large doses and daily Amigen infusions. There was a mild improvement, as noted by a decrease in the number of stools per day, and a 7 pound weight gain. When the Amigen was stopped, there was an abrupt return to her previous condition. A second oral glucose tolerance test was again flat, (Figure 3, Curve B). Repeated urinalyses at no time revealed glycosuria. An 8 day course of corticotropin, 50 mg. per day, was started December 3, 1951 given in an intravenous drip. Following this the patient was started on 75 mg. of corticotropin per day intramuscularly in 4 equally divided doses. There was rapid clinical improvement with a decrease in the diarrhea and gradual weight gain. The dosage of corticotropin was gradually lowered until January 5, 1952 when she was started on corticotropin gel, 40 mg. per day. An oral glucose tolerance test (Figure 3, Curve C) on January 11, 1952 revealed markedly improved absorption; indeed, the character of the curve was suggestive of diabetes. There was no glucose in any of the fractional urine specimens collected during the course of the test.

The patient was discharged to a convalescent home on January 21, 1952. At this time, the patient was asymptomatic, having one bowel movement per day. She gained 24½ pounds during her hospital stay, weighed 114½ pounds at the time of discharge. Glycosuria was noted one week later, while the patient was receiving 50 mg. of corticotropin gel a day. For the next six days, fractional urine specimens showed glycosuria ranging from zero to 10 per cent. The morning urines were sugar free, with the late afternoon and evening specimens showing the greatest amounts.

On February 2, 1952, while still on 50 mg. of corticotropin gel per day, a fasting blood sugar was 125 mg. per 100 cc. A 24 hour collection of urine from February 4 to February 5 showed 60 gm. of glucose in a volume of 1500 ml. An oral glucose tolerance test (Figure 3, Curve D), on February 5, 1952 revealed figures of 77, 132, 161, 157 and 125 mg. per 100 cc. for the fasting, half hour, one, two and three hour specimens respectively. Fractional urine determinations during the course of this test were negative for sugar at the fasting and half-hour periods, less than ¼ per cent sugar at the first hour and ¼ per cent at the second and third hour periods. From the time that glycosuria had first been noted, the patient had no polyuria, polydypsia, weight loss or other symptoms of diabetes.

The patient continued on corticotropin gel in decreasing doses with persistent glycosuria in her 24 hour urine collections although the percentage of sugar decreased as the dosage was lowered. On 15 mg. of corticotropin gel per day, the patient became aglycosuric. A glucose tolerance test, performed while she was receiving 15 mg. of corticotropin gel daily, was normal (Figure 3, Curve E).

Comment A 43 year old woman with clinically established nontropical sprue resistant to the accepted forms of therapy was given a course of corticotropin with dramatic improvement. A short course of cortisone therapy, given 2½ months before the present admission was not associated with glycosuria or hyperglycemia. There was a family history of diabetes mellitus.

Two oral glucose tolerance tests prior to therapy with corticotropin gave evidence of marked impairment of absorption. Thirty nine days after the initiation of corticotropin, an oral glucose tolerance test was highly suggestive of diabetes, as was a second tolerance test three weeks later. Glycosuria was noted 54 days after the onset of therapy, ranging up to 10 per cent. As the dosage of the drug was reduced, the glycosuria gradually diminished and disappeared when the patient was on 15 mg. of corticotropin per day. A glucose tolerance test at this time proved to be normal.

*Case 5** S. B., a 54 year old white woman, developed the clinical picture of pemphigus vulgaris, confirmed by skin biopsy, in November 1950. Her mother is known to have diabetes mellitus, but there has been no indication of glycosuria or hyperglycemia in this patient's past history.

A course of cortisone therapy ranging in dosage from 200 to 100 mg. per day, was initiated on December 9, 1950 and continued for 16 days. This was followed by a 200 day course of corticotropin, with but a few brief interruptions and two periods of 3 and 9 days respectively, in January and May 1951 when both cortisone and corticotropin were administered.

No glycosuria was noted during the initial period of cortisone treatment. A fasting blood sugar on December 27, 1950, two days after the onset of corticotropin therapy, was 100 mg. per 100 cc. Twenty-three days after the start of corticotropin treatment, on a dose of 120 mg. per day, glycosuria was first noted and her fasting blood sugar was 148.

Intermittently over the next five months, the patient showed occasional mild glycosuria. In July 1951, glycosuria increasing up to 4 plus and acetonuria devel-

*This case was made available to us through the courtesy of Drs. George Baehr and Henry Horn, New York City.

oped. At this time the patient had an acute psychotic reaction and required forced feedings because of her refusal to eat. Despite the forced feedings, her intake was minimal and it was thought that the acetonuria was due, in part, to the poor food intake. The patient continued to receive 100 mg. of corticotropin daily and NPH insulin, in doses up to 70 units, was started twelve days after this increase in glycosuria. For five days there was no effect on the glycosuria but the acetonuria decreased. At this point the corticotropin had to be discontinued because of the persistence of the psychotic reaction. Insulin therapy was continued for an additional five days, by which time the patient was aglycosuric. Over the ensuing six months she was given intermittent courses of corticotropin in small doses, and during these periods showed small quantities of sugar in the urine from time to time.

Comment A 54 year old woman with pemphigus vulgaris was treated wiith a short course of cortisone and prolonged courses of corticotropin. Her mother was known to have diabetes mellitus. During treatment with cortisone a fasting blood sugar was normal and there was no glycosuria. Twenty-three days after the start of corticotropin therapy, a mild glycosuria and hyperglycemia developed. Marked glycosuria and acetonuria, requiring insulin for partial control, developed after 6 months of almost continuous hormonal treatment. Since then mild glycosuria has been present intermittently when the patient received corticotropin therapy in small maintenance doses.

GENERAL COMMENT

The term steroid diabetes was introduced by Ingle and his co-workers[1-4] to describe the type of diabetes induced by the administration of compounds B, E, F, and corticotropin in rats. The characteristic features which distinguished this form of diabetes from pancreatic diabetes were 1) insensitiveness to insulin; 2) striking diminution of the glycosuria with fasting in the absence of insulin; and 3) negative nitrogen balance as a feature of the known catabolic effects of these hormones on nitrogen metabolism, even in mild types of this form of diabetes.

Conn and others[5] induced transient diabetes with short courses of corticotropin in normal humans who exhibited the features of relative insulin insensitivity and a negative nitrogen balance. Sprague and others[6] studied a case of Cushing's syndrome in a boy of 15 who presented marked excretion of 17-hydroxycorticosterone (compound F), insulin insensitivity, negative nitrogen balance in the absence of considerable glycosuria, and a prompt alleviation of the glycosuria by fasting. They assumed that all features found in this case might be based on the secretion of compound F by the hyperplastic adrenal tissue found at autopsy.

Since the introduction of corticotropin and cortisone many thousands of patients have received this form of therapy for a wide variety of diseases. Various observations concerning the effect of this form of treatment upon carbohydrate metabolism have been reported in patients with and without diabetes mellitus.[10, 11, 12] In the patients reported in this study, the development of hyperglycemia and glycosuria represented no obstacle to the continuation of hormonal therapy. This observation is in agreement with that of others.[10, 12]

It is of interest to compare the observations in this group of patients with the known criteria for steroid diabetes. In all our patients glycosuria and fasting hyperglycemia developed during the course of therapy with these hormones. During hospitalization, none of them presented glycosuria or hyperglycemia prior to the institution of therapy. In all, the signs of diabetes disappeared with the discontinuation of therapy or with reduction of the dosage of the drug to minimal levels, i.e., patients 1 and 5 showed no glycosuria or fasting hyperglycemia with dosages of 10 mg. corticotropin per day. There was a correlation between the extent of the glycosuria and the dosage level of these hormones. Elevation of the dose resulted in increased glycosuria, diminution of the dose was followed by decreased glycosuria in the same patient.

The group, as a whole, presented all the known features of steroid diabetes but for the response of glycosuria to fasting in the absence of insulin. No attempt was made to investigate this characteristic of steroid diabetes. Case 1 showed a relative resistance to insulin in that dosages of up to 110 units per day came far from controlling the glycosuria. However, with the reduction of the corticotropin dosage glycosuria rapidly subsided and even with small doses of corticotropin, glycosuria was absent and insulin treatment was not needed. Later in the follow-up study of this patient, while on 5 to 10 mg. of corticotropin daily, the urine was persistently negative for sugar and the character of the glucose tolerance curve was normal. Case 5 showed a similar insulin insensitivity with very little effect of daily doses of 60-70 units of insulin on her glycosuria, but rapid and complete subsidence of the glycosuria on discontinuation of corticotropin treatment. However, the patient in Case 3, whose glycosuria per-

sisted after discontinuation of treatment, responded promptly to a short course of insulin. Patients in Cases 2 and 5 showed disappearance of their glycosuria on discontinuation of treatment without the need for insulin. Ketonuria was observed only in Case 5. It must be mentioned, however, that at the time of the development of the marked glycosuria and ketonuria, this patient became psychotic with a food intake limited to a minimum despite forced feeding.

Nitrogen balance studies could be performed only in Case 1. Despite a very high protein intake there was a slight negative nitrogen balance prior to the introduction of insulin treatment. This is in agreement with the known anti-anabolic or catabolic effect of these hormones.

The determination of urinary 17-ketosteroids in Case 2 was low prior to the institution of the second course of corticotropin and remained low during this second course. The findings of diminished adrenocortical function has been observed in diabetes on the basis of lowered excretion of 17-ketosteroids[13] and of 11-17 oxysteroids[14] and by diminished eosinophile response to the stress of surgery.[15]

The most striking common feature in all our patients was their predisposition to diabetes mellitus. This was evidenced by the known cases of diabetes amongst close relatives of patients 1, 2, 4 and 5. Patient 3 had a history of glycosuria ten years prior to the use of hormonal therapy and showed an impaired glucose tolerance one year after the cessation of cortisone treatment. It is probable that in all these patients a primary deficiency of insular function was enhanced by the administration of the pituitary and adrenal hormones. In this connection it may be recalled that the patient reported by Sprague and others likewise had a positive family history of diabetes; at autopsy there was evidence of depletion of the beta granules in the islet tissue of the pancreas stained by the Gomori technique. Only recently Berger[16] demonstrated that 100 mg. of corticotropin given one hour prior to an oral glucose tolerance test resulted in impairment of the tolerance in nondiabetic siblings of known diabetics in contrast to a control group without any family history of diabetes. Prior to Berger's observations, Zucker[17] had produced diabetes with corticotropin in rabbits who were pretreated with nondiabetogenic doses of alloxan.

It is of interest that 4 of our patients developed their glycosuria and hyperglycemia while on corticotropin, and only patient 3, who might have been a diabetic prior to the institution of treatment, showed diabetes while receiving cortisone. Patients 1, 2, 4 and 5 received courses of cortisone without developing any evidences of glycosuria or hyperglycemia before they received their courses of corticotropin. This observation might be explained by differences in the mechanism of the action of these two hormones on carbohydrate metabolism; the stimulation of the adrenal cortex by corticotropin results in an increased production of compound F which seems to have a stronger effect on carbohydrate metabolism than compound E. Differences in the relative dosage must also be considered. In a girl, age 10 years with no known family history of diabetes, studied by Bunim and others,[12] glycosuria and an abnormal glucose tolerance test developed with both cortisone and corticotropin. It is striking, however, that the fasting blood sugar in their patient remained persistently normal (56 to 117 mg. per 100 cc.). In two normal rabbits, Kobernick and More[18] produced considerable hyperglycemia with large doses of cortisone resulting in pathologic changes in the islets of Langerhans. Ingle and others[19] produced glycosuria with acetonuria in force-fed rats with extremely high doses of cortisone.

Although the majority of reports concerning the development of glycosuria and hyperglycemia in man under corticotropin and cortisone treatment may be explained by the assumption that these patients develop diabetes, it must not be overlooked that these hormones may cause alterations in the renal mechanism for the reabsorption of glucose.[11b, 11c] Kass and others[11a] discussed these mechanisms and presented a case recovering from pneumonia during treatment with corticotropin who developed glycosuria. His fasting blood sugar and an intravenous glucose tolerance test were normal and the assumption that this was renal glycosuria appears justified. Patient 4 who had a persistently normal fasting blood sugar level and whose glucose tolerance test was mildly diabetic excreted excessive amounts of glucose, up to 10 per cent, in the absence of polydipsia, polyuria and weight loss. We are inclined to believe that in this case, in addition to a mild steroid diabetes, a significant lowering of the renal threshold for glucose might have accounted for the large quantities of glucose excreted in the urine.

The observations on the clinical features of steroid diabetes in man, as presented in the case of Sprague and others[6] and our own studies may be helpful in explaining the nature of certain manifestations of diabetes mellitus. It is well known that predisposed individuals may exhibit hyperglycemia and glycosuria accompanying fractures, infections, myocardial infarction, burns

and emotional trauma. These manifestations of diabetes may disappear completely and appear many months or years later in the course of a new stress situation. Since corticotropin administration is a form of chemical stress, the possibility must be considered that these "episodes" of hyperglycemia and/or glycosuria may represent instances of steroid diabetes. Similarly, the changes found in well-established diabetics during infections, burns and other stress situations may be an expression of steroid stimulation superimposed on pancreatic insular insufficiency. The negative nitrogen balance and the resistance to insulin so characteristic of these episodes could be easily explained on this basis.

SUMMARY

Five patients who were treated with corticotropin and/or cortisone developed diabetes, the character and course of which were compatible with the features of steroid diabetes.

All patients studied were predisposed to diabetes mellitus. In four, diabetes was known to be present in immediate family members, and in one there was a questionable history of glycosuria ten years previously.

None of the patients had fasting hyperglycemia or glycosuria while hospitalized prior to the institution of hormonal therapy. Diabetes disappeared in 4 patients after therapy was terminated, or after the dosage had been reduced to minimal maintenance levels. In the fifth patient, who had a transient glycosuria 10 years prior to treatment, an abnormal glucose tolerance test was present one year after the cessation of hormonal therapy.

Corticotropin seemed to have a more potent diabetogenic effect. Four of the patients received both hormones, but diabetes was observed only during the administration of corticotropin. The fifth patient, who developed diabetes under cortisone therapy, was suspected of having subclinical diabetes mellitus.

It is suggested that impairment of carbohydrate tolerance developing in well established diabetics under stress situations may represent instances of steroid diabetes precipitated by overactivity of the pituitary-adrenal mechanisms and superimposed on pancreatic insular insufficiency.

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DISCUSSION

DOCTOR PETER H. FORSHAM (*San Francisco, Calif.*): There is little to add to this most stimulating and valuable contribution, other than to reinforce some of the points made by the authors.

It appears to me that the significant fact is not the number of times that diabetes is induced by coricotropin and cortisone therapy, but rather the *rarity of its occurrence.* In an odd 500 patients that I have personally seen under continued therapy for more than one week, with the usual therapeutic dosage of corticotropin and cortisone, I have seen only one case of diabetes mellitus develop. In contrast, moderate glycosuria without high fasting blood sugars occurred in half a dozen or so.

What has been emphasized by the authors is of great importance, namely the *predisposition of patients* to the development of diabetes on steroid therapy, when there is a family history of diabetes. Four out of five of these patients had such a history. It is entirely fair to postulate that a familial deficit in the potential reserve of the islands of Langerhans predisposes to the development of diabetes under continued stress, because of increased adrenal steroid secretion, a rise in diabetogenic pituitary factors or simply repeated hyperglycemia.

Ever since the pioneer work by Homans in 1916, it is well established that the experimental production of diabetes requires removal of at least 4/5 of the islands of Langerhans. We presented evidence before this society two years ago that the occurrence of the diabetic state in patients with Cushing's syndrome was not related to the severity of the osteoporosis or the urinary steroid output, but appeared to be a function of an independent factor, presumably *the state of the islet tissue.* With a deficiency in islet cell reserve the diabetogenic action of the 11-17 oxysteroids is extreme. The relative adrenal cortical insufficiency which we were able to demonstrate in diabetics two years ago, and which has since been confirmed by the work of Field and Marble, thus represents a very useful adaptation of the average diabetic.

After hearing today's paper, one might justly raise the question as to whether one should use these agents, steroids and corticotropin, in patients with a known diabetic history and also in patients with established diabetes. The answer is yes; if and when these agents represent the drug of choice and the only one known to control the disease. Provided that adequate insulin is given, the risk is small. You will recall that one case of the five showed a diabetic blood sugar curve one year after discontinuance of therapy. I would feel that, in this case, the brief period of therapy is analagous to any intercurrent infection which, at this time, might have precipitated permanent diabetes against a background of potential deficiency, such as we find all the time in our diabetic practices. The production of permanent diabetes in a case where corticotropin and cortisone are life-saving is a calculated, but small, risk. A patient with periarteritis nodosa, Doctor Root's patient on whom I was asked to institute first corticotropin and then permanent cortisone therapy, has now lived for more than two years since the beginning of therapy, and while on maintenance with 75 mg. of oral cortisone today, he requires only 10 to 20 units more than he took before the onset of his nearly fatal illness.

Since ketonemia and ketonuria are minimal and often absent in corticotropin- or cortisone-induced diabetes and since the usual sodium loss, which accompanies consistent high blood sugars, is counteracted by the effect of the adrenal steroids on the renal tubules, there is little danger of marked dehydration in a patient with steroid diabetes, provided that he has an adequate water intake so as to make up his water deficit due to the osmotic diuresis of the urinary sugar. The same argument holds for cases who, because of lower thresholds, lose considerable amounts of sugar in the urine.

As to the analogy drawn by the previous speaker between the usual stress situation in the diabetic and during corticotropin treatment, both leading to a deterioration of the diabetic state, one should not ignore the diabetogenic activity of the anterior pituitary in this connection, which both in animal experimentation and in clinical experience appears to be a much more diabetogenic factor than the adrenal steroids.

It would be of interest to know, roughly, from how many treated cases this remarkable series was drawn.

DOCTOR BOOKMAN (*concluding*): I do not know the exact number of patients from which this series was drawn, but it is well over 500. This would fit in with Doctor Forsham's figure of less than 1 per cent of individuals developing diabetes of this extent.

Regarding the age distribution, these patients are all in the middle age group, the youngest being about 40 and the oldest about 60.

Insofar as the development of permanent diabetes is concerned, we do not feel at all sure that the one individual who showed a positive glucose tolerance test one year after treatment developed it as a result of his treatment. As I said, he had a previous history of glycosuria, and a very mild impairment of his glucose tolerance after treatment had been stopped.

I would emphasize, and agree with Doctor Forsham, that we do not feel the development of diabetes is a contraindication to treatment with these drugs, if it is indicated for treatment of the patient's basic disease.

EFFECTS OF ANTEROR PITUITARY EXTRACTS AND OF GROWTH HORMONE PREPARATIONS OF THE ISLETS of LANGERHANS and the PANCREAS

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Unlike endocrine glands which are under a pituitary tropic influence, the pancreatic islets do not atrophy within a period of several weeks following hypophysectomy.[11] Nevertheless there is good evidence that under certain circumstances extracts of the pituitary gland may exert stimulating effects on the islets of rats. Anselmino, Herold and Hoffman[1] first reported that an extract of the anterior pituitary gland administered to rats led to an increase in islet tissue. Using a different anterior pituitary extract, Richardson and Young[2] found that there was a large increase in the islet to acinar ratio in the pancreas. Marks and Young[3] later showed that repeated injections of an anterior pituitary extract led to an increase in the insulin content of the pancreas of the rat. Young[4] found that with repeated injections of a diabetogenic extract in dogs, the diabetes disappeared after a few days but reappeared when the dose was increased. The pancreases of these dogs showed proliferative changes in the islets and the author suggested that there was in the extract, in addition to the diabetogenic material, a more slowly acting pancreatropic factor which led to proliferation of the islet cells and increased insulin production. Proliferative changes in islets, acini and ducts of the pancreas in dogs injected with diabetogenic pituitary extracts were reported by Ham and Haist.[5] The influence of age on the effect of pituitary injections was pointed out by Mount,[6] who reported that a fresh saline extract of the anterior pituitary gland or a "Prolactin" solution tended to have a relative islet-increasing effect in mice 55 days old, but that this was largely absent in mice 95 days old. Krichesky[7] concluded that hypophysectomized rats showed an increase in islet tissue which was reduced again by the administration of pituitary extract. Adams and Ward[8] found similarly that the total number of islets increased in hypophysectomized newts and that administration of anterior pituitary extract tended to prevent the increase, though in normal animals the pituitary administration elevated the islet numbers. An apparent increase in islet volume and islet numbers may arise from the fact that there is a great reduction in the acinar tissue of the pancreas following hypophysectomy, this change leading to a large increase in the concentration of islet tissue in the pancreas. The effects of anterior pituitary extracts in hypophysectomized animals reported by Krichesky,[7] and Adams and Ward,[8] might conceivably result from a stimulating action of the extracts on the acinar tissue. However, in view of the

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reported effects of anterior pituitary extracts in intact rats, one might anicipate that such extracts would stimulate rather than depress the islets in hypophysectomized animals.

Since much of the information in the literature concerning the effects of anterior pituitary extracts on islet volume relates to intact animals, and the reported results of pituitary injections in hypophysectomized rats appear to be somewhat out of harmony with those obtained in the intact animals, it seemed desirable to investigate the influence of pituitary extracts on the total islet weights in intact and hypophysectomized rats. Following this, it was of interest also to investigate the effects of purified growth hormone preparations in intact and hypophysectomized animals.

MATERIALS AND METHODS

Intact male rats of the Wistar strain, and hypophysectomized and intact female and male rats of the Sprague-Dawley strain, were injected with crude saline extracts of the anterior pituitary gland prepared after the method of Schockaert.[9] In the first experiments the extract was prepared every third day from frozen glands. In the second experiment the extract was lyophilized and kept in the dried state. In the third experiment the extract was frozen quickly and preserved in the frozen state. A few tests were run also using a globulin fraction of the anterior pituitary gland provided through the kindness of Mr. D. W. Snair. Control animals were fed *ad libitum* except in the experiment with hypophysectomized rats when paired-fed controls were used in addition to the controls fed *ad libitum.* Test and control rats were sacrificed at the same times. Islet volumes were estimated by a slight modification of the method of Haist and Pugh.[10]

Three purified growth hormone preparations supplied through the courtesy of Armour and Company and one purified growth hormone preparation supplied through the courtesy of Frank W. Horner and Company were injected into hypophysectomized and intact rats of the Sprague-Dawley strain. A small amount of growth hormone preparation used for preliminary tests was supplied through the kindness of our colleague, Dr. J. Campbell. Control rats fed *ad libitum* were used for most of the experiments since the test animals ate more than the controls. In two series, the injected intact rats were paired-fed with the controls. In the series in which hypophysectomized animals were injected with anterior pituitary extracts or with growth hormone preparations, paired-fed controls were used also.

EXPERIMENTAL RESULTS

The effect of crude saline extracts of the anterior pituitary gland on the islet weight:

Table I shows the results of daily injections into intact male rats of freshly prepared crude saline extracts of the anterior pituitary gland and of reconstituted lyophilized saline extracts, in amounts equivalent to 2 gm. of the fresh gland, for periods of 22 to 50 days.

It is evident from this table that the islet weight is increased as a result of the injections of these crude pituitary extracts ($p<.001$). However, the body weight also increased and the pancreas weight was elevated somewhat. Nevertheless, there is an increase in the islet weight per 100 gm. body weight ($p<.001$) and in the percentage of islet tissue in the pancreas ($p<.01$) showing that the increase in islet tissue is out of proportion to the increase in body weight or pancreas weight.

The effect of a globulin extract of the anterior pituitary gland:

Table 2 shows the results of the daily injections of a globulin fraction of the anterior pituitary gland, rich in growth factor, into male rats for periods of 14 to 48 days.

From this table it will be seen that the injection of a globulin extract of the anterior pituitary gland increases the weights of the islets of Langerhans above those of the control animals in each instance. However, the increase in body weight is also much greater than in the controls and as a result the islet weight per 100 gm. body weight is not much altered. These results are too few and the differences are not statistically signicant. Nevertheless the findings are suggestive.

The effects of the injection of anterior pituitary extract in hypophysectomized rats:

The effect on the islet weights of injecting a saline extract of the anterior pituitary gland daily for periods of 41 to 73 days into hypophysectomized female Sprague-Dawley rats is shown in Table 3. Islet weights in paired-fed intact uninjected rats, in hypophysectomized uninjected controls and in intact controls fed *ad libitum* are also shown.

From this it would appear that the injection of a crude saline extract of the anterior pituitary gland into hypophysectomized rats had caused the islets to increase in weight ($p<.01$). The values are similar to those in normal paired-fed uninjected controls. The percentage of islet tissue in the pancreas is similar to that in the hypophysectomized rats and higher than in the intact

TABLE I The effect of crude saline extracts of the anterior pituitary gland on the islet weights in intact male rats. Standard deviations are shown following the mean values.

Group	No. of rats	Mean Body weight Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 / pancreas wt.	Mean islet weight per 100 g. body weight mg.
1. Fresh APE 22-43 days.	5	183±51	271±71	0.970±0.220	11.7±2.8	1.22±0.24	4.4±0.82
2. Controls fed ad libitum.	4	168±48	233±50	0.753±0.182	7.0±1.6	0.93±0.03	3.0±0.32
3. Dried-reconstituted APE 42-50 days.	5	134±18	334±28	1.160±0.137	15.2±1.3	1.32±0.20	4.6±0.47
4. Controls fed ad libitum.	5	131±18	291±31	0.946±0.081	9.4±2.0	0.99±0.19	3.2±0.45
5. All APE injected.	10	159±45	302±61	1.065±0.200	13.4±2.8	1.27±0.21	4.5±0.63
6. All controls.	9	148±38	265±48	0.860±0.162	8.3±2.1	0.96±0.20	3.1±0.42
t values for 1 and 2 (by groups)				1.58	2.94**	2.37*	3.29**
t values for 3 and 4 (by groups)				3.0**	5.52***	2.7**	4.51**
t values for 5 and 6 (by groups)				2.43*	4.50***	3.27**	5.46***

* probably significant ($p<.05$) ** significant ($p<.01$) *** highly significant ($p<.001$)

Calculations of significance, including all animals, show that injections of crude anterior pituitary extracts increase the weight of the islets of Langerhans ($p<.001$), the percentage of islet tissue in the pancreas ($p<.01$), the islet weight per 100 g. body weight ($p<.001$) and probably the pancreas weight ($p<.05$).

TABLE II The effect of a globulin extract of the anterior pituitary gland injected into male rats.

Group	Duration Days	Body weight Initial gm.	Final gm.	Pancreas weight gm.	Islet weight mg.	Islet x 100 / pancreas wt.	Islet/100 g. body weight mg.
Injected 1 cc./day.	14	134	187	0.563	6.6	1.17	3.5
Control.	15	128	156	0.724	4.9	0.68	3.2
Injected 1 cc./day.	21	141	228	0.799	7.4	0.93	3.2
Control.	26	138	210	0.643	5.6	0.87	2.7
Injected 2.5 cc./day.	35	110	318	0.837	13.5	1.61	4.3
Control.	41	118	243	—	—	—	—
Injected 3.0 cc./day.	43	208	435	1.342	15.4	1.15	3.5
Control.	48	212	268	0.793	9.5	1.20	3.5

TABLE III The effect of crude anterior pituitary extract (APE) in hypophysectomized female rats (41-73 days). Standard deviations are shown following the mean values.

Group	No. of rats	Body weights Initial gm.	Body weights Final gm.	Pancreas weight gm.	Islet weight gm.	Islet x 100 / pancreas wt.	Islet wt. per 100 g. body wt. mg.
1. Hypox.	4	111±2	122±7	0.230±0.021	3.7±0.8	1.63±0.50	3.0±0.56
2. Hypox. injected with APE.	7	119±3	240±19	0.488±0.060	6.8±1.7	1.40±0.29	2.8±0.68
3. Paired-fed controls (for 2)	7	120±	216±24	0.860±0.120	7.4±2.4	0.85±0.18	3.4±0.99
4. Ad lib. controls.	4	132±9	291±8	1.070±0.059	9.9±1.2	0.93±0.11	3.4±0.43
t values for 1 and 2			11.9***	8.15***	3.48**	0.98	0.40
t values for 2 and 3 (compared by pairs)			4.2**	10.46***	0.88	5.86***	2.03
t values for 2 and 4			5.1***	15.6***	3.25**	3.06**	1.48
t values for 1 and 4			32.8***		8.53***	2.76*	1.14

*probably significant ($p<.05$); **significant ($p<.01$); ***highly significant ($p<.001$).

The calculations show that the injection of APE into hypophysectomized rats significantly increased the body weight above that of the uninjected hypophysectomized rats ($p<.001$) and above that of the paired-fed controls ($p<.01$) but that this weight was less than that of controls fed ad libitum. The pancreas weights were significantly increased by the injections of APE ($p<.001$) but the pancreas weights in the injected hypophysectomized animals were significantly less than in the paired-fed control group ($p<.001$) or the ad lib. control groups. The islet weight was significantly increased in the injected group ($p<.01$) but there was no significant difference in the islet weight between the hypophysectomized-injected rats and their paired-fed controls though the injected rats had less islet tissue than the controls fed ad libitum.

The islet x 100/pancreas ratio was not significantly different in the hypophysectomized and hypophysectomized-injected rats, but in the hypophysectomized-injected rats it was greater than in the paired-fed controls or control rats fed ad libitum. No significant differences in islet weight/100 g. body weight were shown.

control rats. The anterior pituitary extract did not restore the pancreas weights completely. The pancreases in the hypophysectomized-injected rats grew, but not as well as in the paired-fed controls even though the body weights in the hypophysectomized-injected groups were, in most instances, higher than in the intact controls. The differences in islet weight per 100 gm. body weight were not significant between hypophysectomized, hypophysectomized-injected and intact uninjected control groups.

This experiment indicates that a crude saline extract of the anterior pituitary gland can exhibit its stimulating effect on the islets in the absence of the pituitary. In the hypophysectomized animal the weight of the pancreas, as a whole, is not completely restored by such injections.

The results obtained with anterior pituitary extracts are shown in Figure 1.

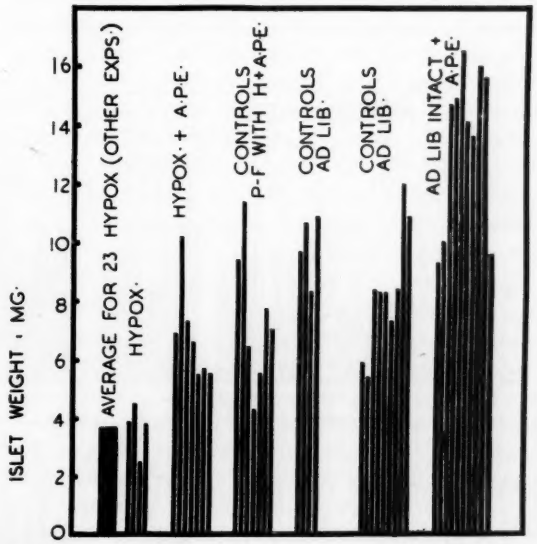

FIGURE 1 Collected islet weights for experiments in which crude saline extracts of the anterior pituitary gland (APE) were injected into hypophysectomized (Hypox) and intact rats. Values are also shown for control rats paired-fed with the hypophysectomized-injected rats and for control rats fed ad libitum.

The effect on the islet weights of injections of purified growth hormone preparations in hypophysectomized and intact rats.

In the experiments on the effects of growth hormone on the islets of Langerhans, hypophysectomized and intact male and female Sprague-Dawley rats were used.

Individaully paired-fed intact rats, intact rats fed *ad libitum* and hypophysectomized-uninjected rats were used as controls for the hypophysectomized-injected animals. Intact rats injected with the growth preparations were usually permitted to feed ad libitum but in some instances were paired-fed with the controls fed ad libitum. The injections were continued for a period of 21 to 28 days. The results of the injections of preparation 22 K R I (Armour and Company) are shown in Table 4. Injections of G-H preparation J-21609 R (Armour and Company) had the effects indicated in Table 5. The values obtained in the experiment using preparation C 3 E-J51 (Frank W. Horner Company) are presented in Table 6. Table 7 shows the effects of the injection of G-H preparation K 40805 R (Armour and Company). All results are combined in Table 8. Individual values are shown in Figure 2.

From the results it will be seen that the injections of each of the growth hormone preparations into hypophysectomized rats caused increases in islet weights above the levels in hypophysectomized uninjected animals. These increases were similar to the increases found in uninjected, intact control animals given the same amount of food. The combined results show that growth hormone preparations when injected into normal intact rats also occasioned significant increases in islet weights above the control values, though these increases were not great.

It is interesting to note too that injections of growth hormone preparations into hypophysectomized rats caused no increase in islet weight per 100 gm. body weight as compared to hypophysectomized-uninjected rats or paired-fed intact controls. However, as evidenced by the combined results, they did cause an increase in the islet weight per 100 gm. body weight when injected into intact rats. The pancreas weights, which were greatly reduced by removal of the pituitary gland, were increased by the injection of growth hormone preparations in the hypophysectomized animals but this increase did not restore the pancreas weights to the levels found in the intact paired-fed controls. No significant changes in pancreas weights were found to result from the injections of growth hormone preparations in intact rats. The high percentage of islet tissue found in hypophysectomized rats was reduced somewhat by the injections of growth hormone preparations but still remained higher than in intact rats.

The body weights of the hypophysectomized animals were increased by the injections of growth hormone preparations. The combined results showed that, in *intact* rats, the injections of growth hormone preparations led to no significant increases in body weight. In only one of the individual experiments was a probably significant increase obtained.

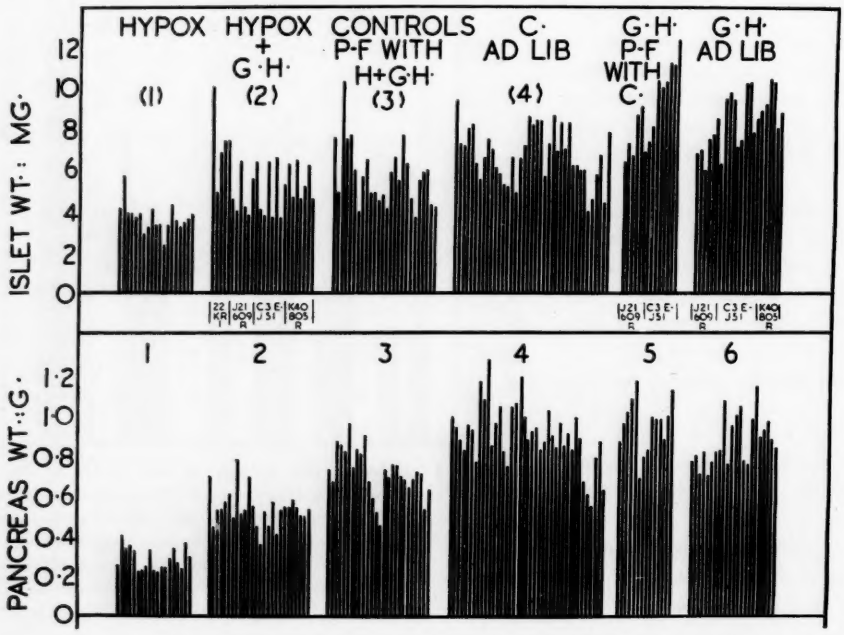

FIGURE 2 Individual islet weights and pancreas weights for experiments in which anterior pituitary growth hormone preparations were used. Hypox = hypophysectomized; G.H. = growth hormone preparations; C = control; P-F = paired-fed.

CONCLUSIONS

The experiments reported here support the conclusion that daily injections of crude saline extracts of the anterior pituitary gland stimulate the islets to grow in intact rats. This confirms the work of other investigators previously mentioned. In hypophysectomized rats the crude saline extracts also caused the islet weights to increase. This is contrary to the previously mentioned reports concerning the effects of pituitary extracts in hypophysectomized animals.

The injection of several different growth hormone preparations also caused an increase in islet weights in hypophysectomized and in intact rats. In the intact rats, the increase was significant but not large. With both the crude anterior pituitary extracts and the growth hormone preparations the increases in islet weights in the hypophysectomized rats were similar to those obtained in intact control rats receiving the same caloric intake. The islet weights per 100 gm. of body weight were not increased by the injections of the anterior pituitary extracts or growth hormone preparations in the hypophysectomized rats. The observed increases in islet weights in the hypophysectomized animals may thus conceivably result from the increased food consumption in the injected hypophysectomized rats, the increase in body weights, and the effect this has on insulin requirements. In the intact animal, both the anterior pituitary extracts and the growth hormone preparations stimulate the growth of the islets to a greater extent than the growth of the body, and not only is the islet weight increased but the islet weight per 100 gm. of body weight is elevated also. Some additional factor, absent in the hypophysectomized animal, would appear to be operating in the intact rat.

Another interesting observation relates to the pancreas as a whole. The great reduction in pancreas weight resulting from the removal of the pituitary gland has been reported before from this laboratory[11] and also by Griffiths[12] and by Koster.[13] It is important to note that while the body weight in the hypophysectomized rats injected with anterior pituitary extract or growth hormone may be significantly grater than in the intact paired-fed controls, the pancreas weight is significantly less than in the control rats. The pancreas is not completely restored by the growth hormone or pituitary injections. This was reported also by Griffiths[12] using a crude anterior pituitary extract. Some further factor not present in the growth hormone preparations appears to be required. Either this factor is absent in the crude extract also, or the animal has become resistant to the necessary factors present in the extract. Because the pancreas weight is not restored completely the percentage of islet tissue in the pancreases of hypophysectomized-injected rats remains higher than in the intact controls.

Though there is a stimulating effect of certain anterior pituitary extracts and principles on the islets, this does not mean that there is a pituitary pancreatropic effect in the same sense as there are thyrotropic, gonadotropic and adrenocorticotropic effects. Atrophy of the pancreatic islets does not occur to any great extent within a period of several weeks following removal of the pituitary gland.[11] Hence the anterior pituitary is not required for maintenance of the islets, though normally the islets fail to grow in its absence.

The means by which the pituitary stimulates growth of the islets of Langerhans in intact and hypophysectomized rats has not been clearly demonstrated as yet. Some of the functions of the anterior pituitary gland are antagonistic to those of the endocrine pancreas and when certain of the products of the anterior pituitary are present in excess, more insulin is required or signs of diabetes are observed. This may be demonstrated in sensitive adult dogs or in partially depancreatized animals of several species. These diabetogenic effects can be prevented by giving insulin. In the *intact rat* the diabetogenic pituitary preparations do not produce diabetes, possibly because the islets in the rat can sufficiently increase their insulin supply. It has been shown in this paper that the islet weight in the rat is increased by injections of saline extracts of the anterior pituitary gland and by injections of growth hormone preparations, both of which are diabetogenic in sensitive adult dogs. The islet increase in the rat may thus be a compensatory response to an increased requirement for insulin. No convincing evidence of a direct stimulating action of anterior pituitary preparations on the pancreatic islets has been obtained However, the pituitary extracts and preparations have effects outside the pancreas which could increase the need for endogenous insulin. The manner in which this increased requirement is transmitted to the pancreas, whether through an increase in blood sugar level, or a reduction in blood insulin level or through the liberation of some other chemical intermediary is not known.

SUMMARY

The weight of the islets of Langerhans in the pancreas was increased by daily injections of a crude saline extract of the anterior pituitary gland, and also by

TABLE IV The effect of 1 mg.: rat: day of growth hormone preparation 22 KR (Armour) on the weight of the islets of Langerhans.

Group	Sex	Number of rats	Mean body weights Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 pancreas	Mean islet wt. (mg.) per 100 g. body weight
1. Hypox.	2F 2M	4	112	109±17	0.341±0.062	4.4±0.8	1.46±0.23	4.1±0.5
2. Hypox.+ GH prep. 22KR 1 (Armour)	2F 3M	5	104	182±25	0.556±0.092	7.4±1.8	1.31±0.13	4.0±0.5
3. Controls P-F with (2).	2F 3M	5	104	176±22	0.789±0.088	7.6±1.9	0.99±0.17	4.3±0.6
4. Controls fed ad lib.	3F 3M	6	108	213±33	0.920±0.058	7.7±1.1	0.84±0.11	3.7±0.7
t values for 1 and 2 (by groups)				4.90**	3.99**	2.92*	1.25	0.27
t values for 2 and 3 (by pairs)				0.19	4.21†	0.27	4.92**	0.92
t values for 2 and 4 (by groups)				1.71	8.06***	0.42	6.75***	0.78

*probably significant ($p<.05$), **significant ($p<.01$), †significant ($p<.02$), ***highly significant ($p<.001$)

Calculation of the t values shows that the hypophysectomized animals injected with growth hormone preparation 22KR 1 (Armour) had significantly higher body weights and pancreas weights ($p<.01$) and probably significantly higher islet weights ($p<.05$) than hypophysectomized uninjected rats. The body weights and islet weights in the injected rats did not differ significantly from those in intact control animals receiving the same caloric intake, but the pancreas weights were significantly higher in the control group ($p<.02$). Injections of this growth hormone preparation did not completely restore the pancreas weights or percentage of islet tissue in the pancreas.

TABLE V The effect of growth hormone preparation J-21609 R (Armour) on the weight of the islets of Langerhans. Mean values are followed by the standard deviation.

hypox=hypophysectomized

Group	Sex	Number of rats	Mean body weights Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet wt. (mg.) per 100 g. body weight
1. Hypox+ GB prep. J-21609 R (Armour)	3F 3M	6	109	184±16	0.602±0.117	4.8±1.0	0.81±0.08	2.6±0.7
2. Controls P-F with (1)	3F 3M	6	109	165±24	0.819±0.011	5.3±0.91	0.67±0.14	3.3±0.7
3. Controls fed ad lib.	4F 3M	7	112	201±48	0.982±0.151	6.3±1.3	0.66±0.16	3.2±0.6
4. Intact inj. GH prep. J-21609 R P-F with (5)	3F 3M	6	119	211±35	0.966±0.167	7.5±1.2	0.79±0.11	3.6±0.3
5. Controls fed ad lib. Sacrificed with (4)	3F 3M	6	116	208±34	0.964±0.242	6.4±0.8	0.69±0.12	3.1±0.4
6. Intact+ GH prep. J-21609 R. Fed ad lib.	3F 3M	6	120	200±21	0.763±0.050	7.3±0.9	0.95±0.11	3.6±0.3
7. Controls fed ad lib. Sacrificed with (6)	3F 3M	6	120	168±23	0.685±0.121	5.2±1.1	0.77±0.09	3.1±0.5
t values for 1 and 2 (by pairs)				1.74	3.18*	1.05	2.87*	1.57
t values for 1 and 3 (by groups)				0.83	4.98***	2.35*	2.18*	1.56
t values for 4 and 5 (by pairs)				0.26	0.03	2.20*	2.33	2.09
t values for 6 and 7 (by groups)				2.46*	1.46	3.57**	3.09†	2.14

*$p<.05$, **$p<.01$, ***$p<.001$. †$p<.02$

Calculations of the t values indicate that the body weights and islet weights in hypophysectomized rats injected with this growth hormone preparation do not differ significantly from the values in paired-fed intact rats. The pancreas weights and percentage

of islet tissue in the hypophysectomized rats are not restored completely by the injection of this growth hormone preparation. Its injection into intact rats led to a significant increase in islet tissue in animals fed ad libitum ($p<.01$) and to a probably significant increase ($p<.05$) in intact animals paired-fed with controls which were fed ad libitum. The injected animals which were paired-fed with the controls showed final body weights similar to the controls, whereas when the injected animals were fed ad libitum a probably significant increase in body weight was observed ($p<.05$). In the latter, also, a significant increase in the percentage of islet tissue in the pancreas was noted ($p<.01$)

TABLE VI The effect of growth hormone preparation, C3E-J51 (Frank W. Horner Co.), on the weight of the islets of Langerhans. Standard deviations are shown following the mean values.

hypox=hypophysectomized

Group	Sex	Number of rats	Mean body weights Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet weight (mg.) per 100 g. body weight
1. Hypox	4F 5M	9	92	103±10	0.257±0.045	3.4±0.5	1.33±0.23	3.3±0.7
2. Controls P-F with (1)	4F 5M	9	91	103±23	0.546±0.060	4.1±0.7	0.78±0.18	4.4±0.16
3. Hypox+ GH (Horner's)	5F 3M	8	91	152±24	0.478±0.073	4.9±1.5	1.00±0.17	3.2±0.89
4. Controls P-F with (3)	5F 3M	8	90	142±20	0.646±0.114	5.7±1.2	0.88±0.10	4.0±0.70
5. Controls fed ad lib.	5F 3M	8	97	216±17	0.901±0.062	7.7±1.0	0.85±0.09	3.6±0.48
6. Intact+ GH prep. (Horner's) P-F with (5)	5F 3M	8	97	218±17	0.948±0.108	10.1±1.6	1.06±0.10	4.7±0.9
7. Intact+ GH prep. (Horner's) fed ad lib.	5F 5M	10	96	219±15	0.891±0.126	8.6±1.4	0.98±0.22	3.9±0.54
t values between 1 and 2 (by pairs)				0.306	8.93***	3.09†	5.82***	2.82*
t values between 1 and 3 (by groups)				5.72***	7.62***	2.85†	3.35**	0.31
t values between 3 and 4 (by pairs)				2.27	4.74**	1.14	1.33	1.63
t values between 5 and 7 (by groups)				0.32	0.07	1.65	1.58	1.57
t values between 3 and 5 (by groups)				6.31***	12.46***	4.38***	2.21*	1.01
t values between 5 and 6 (by pairs)				0.35	0.94	3.25†	3.73**	3.08†

*** $p<.001$ ** $p<.01$ † $p<.02$ * $p<.05$

Calculations of the t values for 1 and 2 show that in hypophysectomized rats the pancreas weights ($p<.001$), islet weights ($p<.02$) and islet/100 g. body weight ($p.<.05$) were less than in paired-fed controls, while the percentage of islet tissue in the pancreas was greater ($p<.001$). Administration of growth hormone preparation to hypophysectomized rats caused a significant increase in body weight ($p<.001$), pancreas weight ($p<.001$) and islet weight ($p<.02$) and a significant decrease in the percentage of islet tissue in the pancreas ($p<.01$). The hypophysectomized-injected rats compared to paired-fed controls had significantly smaller pancreases but the differences were not significant for body weight, islet weight, islet weight per 100 g. body weight or percentage of islet tissue in the pancreas. Intact animals injected with GH preparation and paired-fed with controls (5 and 6) showed an increase in islet tissue ($p<.02$) islet weight per 100 g. body weight ($p<.02$) and percentage of islet tissue in the pancreas ($p<.01$), though the rats injected with GH preparation and fed ad libitum showed no significant changes.

daily injections of growth hormone preparations, in hypophysectomized and in intact rats. In the hypophysectomized rats this increase was proportional to the increase in body weight, whereas in the intact rats it was relatively greater.

The pancreas weight, greatly reduced following hypophysectomy, was partially though not completely restored by the administration of growth hormone preparations or of crude saline extracts of the anterior pituitary gland.

The percentage of islet tissue in the pancreas, greatly increased by hypophysectomy, was reduced somewhat by daily injections of growth hormone preparations or of crude saline extract of the anterior pituitary gland, but the percentage of islet tissue in the pancreas of the hypophysectomized-injected animals remained higher than in control rats.

The growth hormone preparations and crude pituitary extracts occasioned an increase in body weight in the hoypophysectomized rats but the effect on body growth was less evident in intact rats.

The results were discussed and the possibilities of indirect or direct effects of the anterior pituitary preparation on the islets of Langerhans were considered.

TABLE VII The effect of growth hormone preparation K 40805 R (Armour) on the weights of the islets of Langerhans.

hypox=hypophysectomized

Group	Sex	No. of rats	Mean body weights Initial g.	Mean body weights Final g.	Mean pancreas weight g.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet wt. (mg.) per 100 g. body weight
1. Hypox	3F 3M	6	99	115±4	0.302±0.046	3.7±0.37	1.24±0.20	3.2±0.31
2. Hypox + GH prep. (K 40805 R, Armour)	3F 4M	7	106	195±24	0.535±0.027	5.5±0.87	1.02±0.16	2.8±0.48
3. Controls P-F with (2)	3F 4M	7	106	157±26	0.655±0.065	4.9±0.92	0.75±0.10	3.1±0.67
4. Controls fed ad lib.	3F 3M	6	105	225±32	0.905±0.061	7.0±1.1	0.78±0.11	3.1±0.2
5. Intact + GH prep. (K 40805 R, Armour)	3F 3M	6	108	243±33	0.944±0.011	9.3±0.9	0.99±0.13	3.9±0.4
t values for 1 and 2 (by groups)				8.06***	11.39***	4.67***	2.13	1.56
t values for 2 and 3 (by pairs)				5.74**	5.37**	1.23	4.62**	1.23
t values for 2 and 4 (by groups)				1.94	14.65***	2.95†	3.05†	1.50
t values for 4 and 5 (by groups)				0.95	0.76	3.83**	3.04†	4.60***

† $p<.02$ ** $p<.01$ *** $p<.001$

Calculations of t values show that injections of growth hormone preparation K 40805 R (Armour) led to a highly significant increase in body weight, pancreas weight and islet weight in the hypophysectomized rat ($p<.001$). The final body weights in the hypophysectomized-injected animals were significantly greater than in paired-fed controls ($p<.01$), but the pancreas weights were significantly less than in the paired-fed controls ($p<.01$) and the islet weights were not significantly different. The high percentage of islet tissue in the pancreas of hypophysectomized rats is not restored to normal by the injections ($p<.01$). The pancreas weights ($p<.001$) and islet weights ($p<.02$) in the hypophysectomized-injected animals were less than in control rats fed ad libitum, but the percentage of islet tissue in the pancreas was higher ($p<.02$). Injections of this growth hormone preparation into the intact animal occasioned a significant increase in islet weight ($p<.01$) and percentage of islet tissue in the pancreas ($p<.02$) and a highly significant increase in islet weight per 100 g. body weight as compared to controls fed ad libitum.

ACKNOWLEDGEMENTS

It is a pleasure to thank Professor C. H. Best for his encouragement in this work. We are grateful also to Armour and Company and to the Frank W. Horner Company for supplying the growth hormone preparations, and to the National Research Council of Canada for their financial support.

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TABLE VIII Summary table of mean values for islet weight, including all growth hormone preparations and both sexes. Mean values are followed by standard deviations.

hypox=hypophysectomized

Group	Number of rats	Mean body weights Initial g.	Final g.	Mean pancreas weight g.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet weight (mg.) per 100 g. body weight
1. Hypox	19	98	108±11	0.289±0.057	3.7±0.7	1.33±0.22	3.4±0.6
2. Hypox + GH	26	102	177±27	0.537±0.089	5.5±1.6	1.02±0.21	3.1±0.8
3. Intact P-F with hypox + GH	26	101	158±25	0.716±0.120	5.8±1.5	0.82±0.17	3.7±0.8
4. Intact + GH fed ad lib.	22	106	220±27	0.873±0.124	8.4±1.4	0.98±0.16	3.9±0.4
5. Intact fed ad lib.	39	109	206±35	0.896±0.155	6.8±1.3	0.77±0.13	3.3±0.6
6. Intact ad lib. controls for 7.	14	105	213±25	0.928±0.160	7.1±1.1	0.78±0.13	3.4±0.5
7. Intact PF with 6 and inj. with GH	14	106	215±25	0.956±0.131	9.0±1.9	0.94±0.17	4.2±0.9
t values for 1 and 2 (by groups)			10.32***	10.61***	4.66***	4.73***	1.38
t values for 2 and 3 (by pairs)			3.02**	7.79***	0.81	5.38***	2.74†
t values for 4 and 5 (by groups)			1.65	0.58	4.64***	5.46***	3.94***
t values for 2 and 5 (by groups)			3.55***	10.64***	3.55***	5.98***	1.19
t values for 6 and 7 (by pairs)			0.48	0.64	3.75**	4.15**	3.53**

* $p<.05$ † $p<.02$ ** $p<.01$ *** $p<.001$

The combined results show that the administration of growth hormone preparations in hypophysectomized rats led to increases in body weight, pancreas weight and islet weight which were highly significant ($p<.001$). The percentage of islet tissue in the pancreas of hypophysectomized rats was reduced by the growth hormone administration ($p<.001$). While the body growth was greater in the hypophysectomized-injected rats than in the paired-fed controls ($p<.01$), the pancreas weights were less ($p<.001$) and the islet weights did not show a significant difference. The islet weight per 100 g. body weight was less in the injected than in the control groups ($p<.02$). The percentage of islet tissue in the pancreases of the hypophysectomized animals was not completely restored by the injection of growth hormone preparations. In the intact rats the injections of growth hormone preparations caused no significant increases in body weight or pancreas weight, but the islet weight, percentage of islet tissue in the pancreas and islet weight per 100 g. body weight were significantly increased.

A Definition of Health

Health, like age, is relative. There are degrees of health just as there are degrees of illness, or intelligence, or equanimity, or beauty. Health is an abstraction or ideal. Perfect health is probably unattainable, though it may be approached. Unfortunately, the antiquated, negativistic definition of health as "that state of existing in he absence of disease" is still to be found in some medical dictionaries. Let us redefine health as having quantitative attributes and perfect health as that state of being in which all the functional capacities of the organism have maximum reserves. Optimum health is affected by age. The adolescent or young adult may have maximum cardiac and muscular vigor, but the intellect has not as yet developed to its peak. By the time intelligence and emotional homeostatis are fully developed, somatic depreciations will have reduced other functional capacities to below optimum levels.

The relativity of health is particularly significant in dealing with mature persons. Normal is a vague and misleading term. The commonest connotation is that "normal" is nearly synonymous with "average". Average health certainly does not imply optimum. Thus, normal health and optimum health are frequently widely divergent.

From *Chronic Illness and Senescence* by Edward J. Stieglitz, M.D., in *The Journal* of the American Medical Association, October 4, 1952

Effects of Environment on Diabetes

A study of partially-depancreatized rats exposed to cold

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This is one of a series of studies of the effects of various stressors upon experimentally induced diabetes in the rat. It is shown that exposure of the rat to cold causes a rapid loss of weight, a rise in the level of urinary nonprotein nitrogen and suppression of the glycosuria. When the anmials were returned to room temperature these changes were reversed.

METHODS

Infection-free male rats of the Sprague-Dawley strain were partially depancreatized at a weight of approximately 275 gm. by the procedure described by Ingle and Griffith.[1] After the animals had recovered from the operation and had reached an average weight of approximately 330 gm., they were placed in metabolism cages and adapted to the force-feeding of a medium carbohydrate diet (Table I) by stomach tube each morning and late afternoon. The technic and diet were modified from those described by Reinecke, Ball, and Samuels.[2] During the period of adaptation to force-feeding, the amount of diet was increased gradually to prevent the development of food shock. The animals were brought to a full feeding of 26 cc. of diet per day on the sixth day. Twenty-four hour samples of urine were collected at the same hour each day (8:00 to 8:30 a.m.) and were preserved with toluene and citric acid (1 gm. per sample) to insure the acidity of the urines for nitrogen analysis. Urinary glucose was determined by the method of Shaffer and Williams[3] and the determination of urinary nonprotein nitrogen (NPN) was by the micro-Kjeldahl procedure.

The animals were maintained in a temperature cabinet which has a range of adjustment from 0° to 40° C.±1°. The cabinet has space for 12 rats to be maintained in metabolism cages, each in an individual compartment.

EXPERIMENTS AND RESULTS

Eight severely diabetic rats were maintained at 26° C. ±1° for a period of several weeks, the temperature was then lowered to 3°±1° for 2 weeks and was then raised to 26° for a second control period of 4 weeks.

During exposure to cold the rats lost an average of 55 gm., there was an accompanying rise in the excretion of urinary NPN and there was suppression of glycosuria. When the rats were returned to room temperature these changes were reversed. The changes from and the return to control values were gradual rather than immediate. The data are summarized in Figure 1.

DISCUSSION

Like many other investgiators, we have been concerned with the metabolic consequences of adrenal cortical activation during exposure to various stressors. It is known that exposure to cold causes activation of the adrenal cortices via the increased discharge of corticotropin from the anterior pituitary.[4] On this basis it might be expected that any nonspecific stressor should cause exacerbation of a diabetic state. Under the conditions of this experiment, exposure to cold brought about a suppression of the glycosuria. One of us[5]

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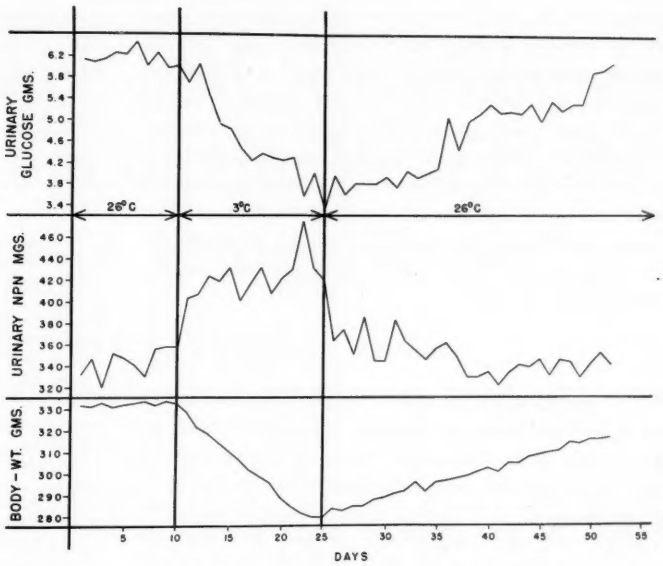

FIGURE 1 Effect of cold upon the partially depancreatized, force-fed rat. Averages for 8 male animals.

(D.J.I.) has reviewed the evidence from this laboratory that nonspecific stressors fail to cause exacerbation of diabetes in the rat. Such observations do not exclude the possibility that activation of the adrenal cortices during stress affects the metabolism of carbohydrate. The metabolic consequences of an increased secretion of adrenal cortical hormones may be masked by other metabolic adjustments during stress such as the increased oxidation of carbohydrate.

When homothermal animals are exposed to low temperature they must either produce more heat or die. Although the ability of the diabetic organism to oxidize carbohydrate for energy purposes is a subject of continuing debate, there is no doubt that these processes are not completely blocked in the partially depancreatized rat even when it is severely diabetic. It seems possible that the oxidation of carbohydrate can be accelerated during a vital need for increased energy in both the normal and diabetic organism. During exposure to cold the diabetic animal may utilize some of the glucose which is wasted into the urine under nonstressful conditions. One of us[6] (D.J.I.) has reviewed the indirect evidence that muscle work can accelerate the utilization of glucose in the diabetic rat. These changes coexist with an increased breakdown of protein and loss of weight which indicates that exposure to cold may also accelerate the mobilization of endogenous tissues for energy purposes. It is possible that gluconeogenesis is accelerated in these animals so that the extent of increased utilization of carbohydrate cannot be determined by measuring changes in the level of urinary glucose alone.

There are other considerations which may require a different interpretation of the results. It was anticipated that the full-blown effect of cold upon glycosuria and upon urinary NPN would be manifest immediately. On the contrary, these changes were gradual. Similarly, it was anticipated that when the temperature was increased to control values (26° C.), the changes in urinary glucose and nitrogen would be immediate, but they also were gradual. The assumption that the metabolic changes are determined by the immediate changes in the energy requirement of the animal may be difficult to reconcile with these data. The decrease in glycosuria became marked only after the animals had lost considerable weight and the glycosuria was restored to control values only after most of the weight had been regained. During recovery from the catabolic phase of the re-

TABLE I MEDIUM CARBOHYDRATE DIET

Constituent	Grams
Cellu flour (Chicago Dietetic Supply House)	60
Osborne & Mendel salt mixture	40
Dried yeast (Pabst)	100
Wheat germ oil	10
Cod liver oil	10
Vitamin K (2-methyl-1,4-napthoquinone)	100 mg.
Mazola oil	200
Casein (Labco)	160
Starch	200
Dextrin	190
Sucrose	200
Water to make total of	2000 cc.

sponse to cold, the animals were able to conserve some of the calories which were wasted as urinary glucose during the control periods. The rates at which the responses to cold wax and wane may be due to inertia in the basic mechanisms (unknown) involved. It can be suggested also that the suppression of glycosuria in rats which have become emaciated during exposure to cold may bear some relationship to the well known but poorly understood effects of emaciation caused by the starvation treatment of diabetes mellitus prior to the introduction of insulin.

SUMMARY

Eight partially depancreatized male rats were maintained on a uniform intake of medium carbohydrate diet by the technic of force-feeding. Following maintenance at 26° C. for several weeks the rats were exposed to a temperature of 3° C. for 14 days. During exposure to cold the rats lost weight and excreted more urinary nonprotein nitrogen. The level of glycosuria decreased during this period. When the temperature was raised to 26° C. for 28 days, the metabolic changes were reversed. The changes during the exposure to cold and during the recovery period were gradual rather than abrupt.

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Quackery in Weight Reduction

While quackery in conjunction with the employment of physical agents for the treatment of obesity is rampant, quackery is by no means limited to physical agents. Reducing pills, vitamin supplements, slenderizing creams, laxatives, candies to be taken just before eating, one-food diets, "Hollywood diets," seven-day and fourteen-day diets of bizarre ingredients have all been widely exploited.

Oliver Feld, in discussing "fooling the fat," has described creams, lotions, and bath powers, which were advertised as miracle agents for reducing weight. He has mentioned also various systems and salons where "rhythmic passive exercise" is claimed to give you the benefits of "active exercise without any of the tiring ill effects." One elaborate string of slenderizing salons" employs such equipment as the "Roaler Massager," the "Back Ring Roller," the "Leg Roller" and the "Modified Slendro Massager," as well as the "Rollo Massage Chair."

It can be commented that careful clinical observation by skilled physicians does not support the claim that any of these mechanical procedures will remove deposits of fat. There is no "easy way" to reduce fat and there is no scientific evidence whatever to indicate that adipose tissue can be made to disappear by massage or by any other means from one region of the body without its disappearing in comparable amounts from other regions.

Innumerable glib claims are made for procedures and devices which are supposed to be effective in "spot reducing" of adipose tissue . . . unscrupulous manufacturers of drugs, proprietors of beauty parlors and physical culture clubs, makers of "slimming creams," and manufacturers of chin straps, reducing belts, massaging devices, rollers, and electrical vibrators have produced almost unlimited claims concerning the value of their devices for "spot reducing."

While the value of nearly all of these devices is absolutely nil, some careful medical observers believe that massage may be of some value after much fat has been removed from the entire body, including the affected region, by appropriate dieting. At this time, massage may aid in restoring elasticity to the sagging skin. However, gentle manual massage is more satisfactory than any of the mehanical devices, rollers or vibrators. The only effective way of reducing fat in local regions of the body except when extremely large amounts of fat are occasionally removed by the heroic measure of surgical excision is to follow a program of general reduction of weight by remaining on a low-calorie diet.

—From *Physical Medicine and Obesity* by Frank H. Krusen, M.D. in *The Journal* of the American Medical Association January 24, 1953

The Incidence and Significance of Degranulation of the Beta Cells In the Islets of Langerhans In Diabetes Mellitus

E. T. Bell, M.D., Minneapolis, Minnesota

It has been known for several years that the beta cells become necrotic or degranulated in experimental diabetes, but it is not so well known that they are often partially or completely degranulated in human diabetes. The purpose of this study is to determine the frequency of degranulation in human diabetes and the conditions under which it occurs. The significance of degranulation will then be discussed.

OBSERVATION OF THE PANCREAS IN AUTOPSY SPECIMENS

A study was made of paraffin blocks of the pancreas obtained at autopsy in 995 cases of diabetes. This group comprised only about two-thirds of the cases in which an autopsy was performed since a paraffin block of the pancreas was not always available in earlier years.

The tissues were all fixed in formalin, and the beta granules were stained with Nerenberg's modification of Gomori's stain for beta granules. With this technic all tissues preserved in paraffin blocks were stained satisfactorily. Tissues preserved in formalin for several months may usually be stained without difficulty, but better results are obtained after shorter periods of fixation.

A well granulated islet is shown in Figure 1, and an islet with complete degranulation in Figure 2. (It is impossible to bring out the beta granules clearly in a photomicrograph without the use of color. Good photomicrographs in color are shown in Plate III of Bell's Textbook of Pathology, 7th Edition, 1952).

In the table, the incidence and the degree of degranulation in diabetes mellitus is shown with respect to the age of death. There was more or less complete degranulation in all diabetic subjects dying under the age of 20 years, and in 79.5 per cent of those dying between the ages of 20 and 40 years. Thereafter there was a progressive decrease in the percentage showing degranulation and only one-third of those who died after 60 years of age showed degranulation of the beta cells.

A group of 250 nondiabetics of various ages, representing a wide variety of diseases was studied. No instance of complete degranulation was found, but in two emaciated subjects the granulation was convincingly reduced. Apart from these two cases, degranulation was found only in cases of diabetes. It may be concluded that the demonstration of this feature is almost certain confirmation of the diagnosis of diabetes mellitus. This is especially helpful in the study of juvenile diabetes in which hyalinization of the islets is rarely found. Another feature, sometimes noted in older diabetics in whom the islets are well granulated, is the presence of occasional giant islets. These structures have a diameter two or three times that of normal islets and they contain few or no beta granules. Fourteen such cases were observed in diabetic subjects over 40 years of age; it appears probable that giant degranulated islets are diagnostic of diabetes.

I have been unable to decide whether there is a decrease of islet tissue in juvenile diabetics, as some

From the Department of Pathology, University of Minnesota, aided by a grant from the U.S. Public Health Service.
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investiagtors have maintained. The random blocks of pancreas available to me do not permit any conclusions.

RELATION OF DEGRANULATION TO THE CLINICAL FEATURES OF DIABETES

Age. It appears in the table, that there is a striking relation between degranulation and the age of the individuals. The islets are usually degranulated in juvenile diabetics, and there is a progressive decrease in the frequency of degranulation up to the age of 60 years. Only about one-third of diabetics over 60 years of age show degranulation.

Sex. Degranulation shows no relation to sex.

The Clinical Severity of the Diabetes. Inasmuch as juvenile diabetes is usually much more severe than diabetes having its onset after middle life there is a suggestion that degranulation is a measure of the clinical severity of the disease. However, when the group over 50 years of age is studied separately, there is no good correlation between granulation and clinical severity. Degranulation is nearly as frequent in subjects who did not require insulin as in those who needed large daily injections. Perhaps this is to be expected, since exogenous insulin relieves the strain upon the pancreas.

The Control of the Diabetes. The overall control refers to the status of the patient up to the time of his terminal illness. I have defined *good control* as meaning freedom from marked glycosuria and other diabetic symptoms without reference to the level of the blood sugar, and *poor control* as meaning the presence of intermittent or continuous diabetic symptoms such as attacks of coma or hypoglycemia, polyuria, weakness, boils and severe glycosuria. Control in this sense shows some relation to degranulation; in the poorly controlled cases in which the patients were over 60 years of age, there was degranulation in 44 per cent, while in only 27 per cent of the well-controlled cases in the same age group was degranulation found. No data are available on subjects in whom the blood sugar was kept rigorously at a normal level.

In the terminal stage of life, diabetes is often out of control in that there is marked glycosuria and hyperglycemia, although previously there had been freedom from such changes. No correlation could be established between the terminal level of the blood sugar and degranulation.

FIGURE 1 Islet of Langerhans from a nondiaebtic, Gomori's stain. Note abundant beta granules. Photomicrograph.

The Cause of Death. In diabetes of older persons, no correlation could be established between degranulation and the cause of death.

It might be anticipated that those dying in diabetic acidosis would show degranulation more frequently but the difference is not impressive. Of 61 subjects over 40 years of age dead of diabetic acidosis, the islets were degranulated in 32 and were granulated in 29.

It appears, therefore, that degranulation is definitely correlated with the age of the subject and to that exent with the severity of the diabetic state. In diabetics over 60 years of age degranulation is not convincingly correlated with any clinical feature of the disease.

THE SIGNIFICANCE OF DEGRANULATION

Best and Haist[1] found that the insulin content of the pancreas of the rat is greatly reduced by fasting, by a diet restricted to fat, and by daily injections of insulin. Insulin injections combined with fasting or fat feeding produce a greater and more rapid decrease of pancreatic insulin. Barron[2] in this laboratory found that rats treated by the above procedures, which reduce the insulin content of the pancreas to low levels, show marked to

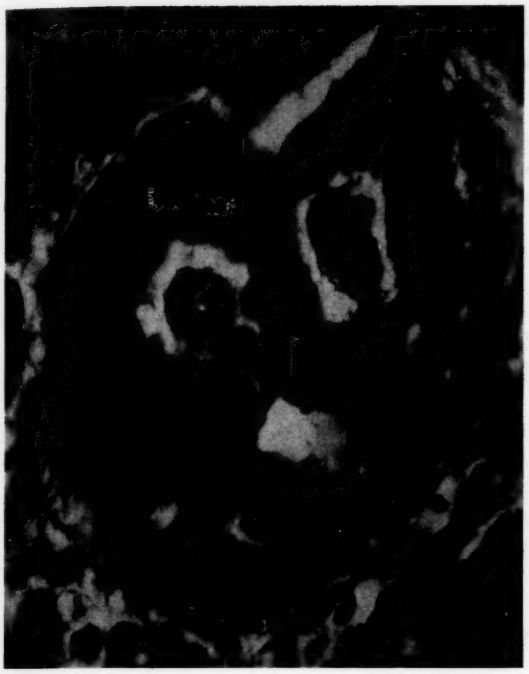

FIGURE 2 Islet of Langerhans from a diabetic subject. Gomori's stain. Note complete absence of beta granules. Photomicrograph.

complete degranulation of the beta cells. We have found repeatedly that daily injections of insulin for one to two weeks in rats will produce complete degranulation of the beta cells. Such animals are temporarily diabetic when insulin is discontinued and they are given a carbohydrate diet. Apparently the pancreas ceases to produce insulin when it is supplied from exogenous sources. This experiment lends strong support to the view that the beta granules represent a precursor of insulin.

Dohan and Lukens[3] produced hydropic degeneration and degranulation of the beta cells in the pancreas of cats by massive intraperitoneal injections of glucose. The blood glucose was maintained at a very high level. Barron and State[4] in this laboratory produced degranulation of the beta cells of the dog pancreas by continuous intravenous infusion of glucose. In experiments of this type degranulation is presumably due to exhaustion of the supply of insulin. No determinations of the insulin content have been made on pancreases degranulated in this way, but the animals are temporarily diabetic.

The experimental evidence suggests that a low insulin content is associated with absence of beta granules.

THE CORRELATION BETWEEN INSULIN CONTENT OF THE PANCREAS AND BETA GRANULES IN HUMAN DIABETES.

Wrenshall, Bogoch and Ritchie[5] have determined the extractable insulin of the pancreas at autopsy in 139 nondiabetic and 64 diabetic subjects. A comparison of my table with their Figure 5 shows a fairly good correlation. In the group under 20 years of age, the extractable insulin is very low and it is quite low in the group 20 to 40 years of age. In the group over 50 years of age the extractable insulin averages about one-half the normal value, but some have a very low and a few a normal insulin content. Their observations on persons under 40 years of age are in close accord with my observations on the beta granules. Their results in persons over 50 years of age may be reconciled with mine if we assume that the beta granules must be reduced about 50 per cent before a convincing degranulation can be recognized in stained preparations.

TABLE 1 Incidence and degree of degranulation of the beta cells in diabetes mellitus.

		Beta Granules				
Age at death	Total Number	Absent	Almost completely absent	Definitely reduced in number	Normal	Degranulation per cent
0-10 yrs.	5	3	1	1	0	100
10-20 yrs.	13	9	3	1	0	100
20-30 yrs.	28	17	4	2	5	82
30-40 yrs.	50	28	3	8	11	78
40-50 yrs.	72	22	7	14	29	60
50-60 yrs.	179	33	11	34	101	44
60-70 yrs.	325	37	15	59	214	34
70-80 yrs.	259	37	15	38	169	35
80-91 yrs.	64	9	0	8	47	27
0-20 yrs.	18	12	4	2	0	100.0
20-40 yrs.	78	45	7	10	16	79.5
40-60 yrs.	251	55	18	48	130	48.2
60-91 yrs.	648	83	30	105	430	33.6
Total	995	195	59	165	576	42.1

With respect to subjects dying in diabetic coma, however, there is a discrepancy. In 8 of their 9 subjects there was an extreme reduction of extractable insulin, while only about one-half of my subjects dying in coma showed degranulation.

On the whole the evidence seems convincing that the beta granules represent a precursor of insulin, and that we may recognize a marked reduction of the insulin content in appropriately stained sections of the pancreas.

In occasional cases the alpha cells are very prominent in the islets of diabetic subjects, but usually they are no more conspicuous than in nondiabetics. The occasional increase in alpha cells in the diabetic pancreas probably represents an anatomical variation rather than a manifestation of diabetes.

THE CAUSE OF DEGRANULATION

There is now abundant evidence that complete degranulation of the beta cells of the islets is associated with a very low content of extractable insulin, and the conclusion seems justifiable that the absence of beta granules means the absence of insulin. Is the decrease of insulin due to a primary disease of the pancreas or to some extrapancreatic influence?

The beta cells may be degranulated experimentally in the following ways:

By alloxan. This chemical substance has a specific toxic action on the beta cells but does not injure the alpha cells. The beta cells either become necrotic and disappear (as in the mouse), or they may persist in a degranulated degenerated state (as in the rat). (In spontaneous human diabetes the beta cells are never necrotic or degenerated and it appears improbable that they have sustained any form of severe injury.)

By sustained hyperglycemia. When the blood glucose is maintained at a very high level for several days, the beta cells become degranulated and the animal is temporarily diabetic. It is believed that degranulation is due to exhaustion of the supply of insulin. In animals with subtotal pancreatectomy, hyperglycemia may cause degeneration and death of the beta cells with the development of permanent diabetes. It appears that the death of the beta cells is due to excessive functional strain since it may be prevented by insulin. (There is no evidence in human diabetes that hyperglycemia causes degeneration of beta cells and we do not know whether high blood glucose is a cause or an effect of degranulation.)

By exogenous insulin. Daily injections of large doses of insulin to rats cause complete degranulation of the beta cells within one or two weeks. When the insulin is withdrawn, the animal is temporarily diabetic, especially when fed a high carbohydrate diet. The beta granules gradually reappear on a normal diet without insulin. Presumably the formation of insulin by the pancreas is influenced by the insulin content of the blood and the pancreas ceases to form insulin when this hormone is supplied from exogenous sources.

By starvation or by diet restricted to fat. When rats are starved or fed only on lard or olive oil the beta cells become completely degranulated.[2] Apparently the beta cells cease to form insulin when there is no carbohydrate available in the food.

By anterior pituitary hormones. There is clinical evidence that the anterior pituitary secretes a diabetogenic hormone, since in acromegaly there is often decreased carbohydrate tolerance and sometimes true diabetes mellitus.

Experimentally, hypophysectomy decreases the intensity of diabetes induced by pancreatectomy. Young[3] has demonstrated that repeated injections of anterior pituitary extract will induce permanent diabetes in dogs by causing degeneration of the beta cells. The injury to the beta cells may be prevented by administration of insulin. The growth hormone has a much stronger diabetogenic action than corticotropin.

In the isolated rat pancreas, Anderson and Long[6,7] found that perfusion with blood having a high glucose content caused a secretion of insulin, but that no insulin was secreted when anterior pituitary extract was added to the perfusate.

This experimental and clinical evidence shows clearly that anterior pituitary hormones are antagonistic to insulin. It is not clear whether this interference takes place in the islets, in the blood or in the tissues. The view that diabetes mellitus is due to overactivity of the anterior pituitary is consistent with our present knowledge.

SUMMARY

The beta granulation of the islets has been studied in 995 pancreases from diabetic subjects. Complete or partial degranulation was found in all subjects under 20 years of age, in 79.5 per cent of those between the ages of 20 and 40 years, in 48.2 per cent of those between the ages of 40 and 60 years, and in 33.6 per

cent of those over 60 years of age.

In diabetics over 50 years of age there is no good correlation between degranulation and the clinical severity of the disease.

In experimental diabetes there is a high correlation between beta granulation and the insulin content of the pancreas. In human diabetes there is a fairly close agreement between the insulin content of the pancreas, as determined by Wrenshall and his associates, and the amount of beta granules which may be stained. It seems well established that the beta granules represent a precursor of insulin.

The beta granules may be removed from the pancreas by excessive functional demand, induced by prolonged severe hyperglycemia or by administration of anterior pituitary extracts. The beta granules also disappear during starvation and when exogenous insulin is administered.

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Experimentation on Human Beings

The Research Worker's Point of View

It is considered axiomatic that the purpose of medical research, perhaps in contrast with more general research, is to discover, improve, or extend information regarding man, his functions, and his relationships to his environment. It follows that a primary scientific criterion of usefulness in medical research is whether the observed phenomena can verily be produced in, or applied to, human beings. Findings on other species may have general or specific validity for man, but the ultimate establishment of such validity must rest in each instance upon direct observations on man. At some point in any medical research, therefore, the investigation must be performed with human beings, if that research is to fulfill its primary objective . . .

Research on human beings, of course, involves unique hazards, precautions, and responsibilities. Whenever human beings are to experiment on human beings, the mores of human conduct, including ethical, religious, and legal considerations, cannot and must not be ignored or minimized.

What then are the proper rules of conduct that can be utilized in judging whether human beings should be involved in experimentation? Perhaps the clearest formulation of such rules was made at the Nuremberg medical trial . . .

Much the same rules in regard to medical experiments on human beings have been delineated by the American Medical Association and by the Green Committee on the use of prisoners in investigations. Analysis of the rules shows that they can be reduced to two primary principles: First, the investigators must be thoroughly trained in the scientific disciplines of the problem, must understand and appreciate the ethics involved, and must thus be competent to undertake and to carry out the experiment, Second, the human experimental subject must understand and voluntarily consent to the procedure, and must not be selected upon any basis such as race, religion, level of education, or economic status. In other words, the investigators and the subjects are human beings with entirely equal, inalienable rights that supersede any consideration of science or general public welfare. Finally, research on human beings is too hazardous and implies too many responsibilities to be undertaken by lone investigators. It should be a group effort supported by a proper consultative body. Experimentation even on oneself without such collaboration and consultation seems as indefensible as similar experimentation on another individual.

From *Experimentation on Human Beings; The Research Worker's Point of View,* By Michael B. Shimkin, in *Science* *117*:205-06, February 27, 1953

(See Page 137 for The Physician's Point of View)

A MODIFICATION OF GOMORI'S STAIN

The Demonstration of Beta Granules in the Islets of Langerhans

S. T. Nerenberg, M.D., Minneapolis, Minnesota

In 1911 Bensley[1] employed special stains to bring out the morphology of the alpha, beta and gamma cells of the pancreatic islets. They work well on guinea pig pancreas. With other species the results are sometimes uncertain. The technic is also difficult. In 1939 Gomori[2,3] introduced a new stain. The technic is much simpler and fails less frequently.

In our experience, while Gomori's stain usually works well on tissues fixed in Bouin's fluid or in formalin, it frequently fails to bring out the beta granules. The failures have been so frequent that one cannot be sure that the beta granules are really absent when the stain fails to show them. Only positive results are dependable. The stain works poorly on tissues preserved in paraffin blocks and usually fails on tissues preserved for some time in formalin. I have attempted to determine the cause of the variations and, if possible, to alter or correct them. I think I have succeeded in simplifying the technic and in increasing the dependability of the stain.

EXPERIMENTAL WORK

On several occasions I observed that when rat tissue failed to take the stain properly, the beta cell granules would stain a faint pink instead of blue. This suggested a change in the *p*H. Gomori recommended Bouin's fixative. This is acid (*p*H 2.1) and seems to inhibit the staining of the beta granules especially on old formalin-fixed tissue. I have also found this fixative unsatisfactory because it makes the tissue very hard to cut, and with a very small piece of tissue, especially with biopsies of the pancreas, it becomes so fragmented that it is difficult to find the islets.

I employed formalin and found that formalin-fixed tissues were easy to cut; thin, even sections could be obtained. Two sets of fixatives were prepared, varying the *p*H. One contained acetic acid, the other ammonium hydroxide. It was found that when the material was fixed with the acetic acid-formalin all the granules, both alpha and beta, dissolved out, while the tissue fixed with the ammonium hydroxide formalin stained well. A number of alkaline salts and alkalis were then tried in the fixative instead of ammonium hydroxide. Ammonium hydroxide and potassium dichromate were found to yield superior results. An objection to ammonium hydroxide was its tendency to cause disintegration if the tissues were left too long in the strongly alkaline solution.

I found with both human and animal tissues that excellent staining of the islets could be secured with the following technic. The tissues were fixed in 4 per cent formalin, cut and then mordanted either in a concentrated ammonium hydoxide 8 per cent-4 per cent formalin solution; or a 16 per cent potassium chromate-4 per cent formalin solution. The use of the 16 per cent potassium chromate-4 per cent formalin mixtures as a mordant yielded excellent results in dealing with human, rodent and guinea pig material. One of the advantages is ease in cutting the fixed tissue on the microtome.

From the Department of Pathology, University of Minnesota. Work done at the suggestion of Dr. E. T. Bell, Emeritus Professor of Pathology, University of Minnesota, and aided by a grant from the U. S. Public Health Service.

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With the above technic, very old human tissues preserved in paraffin blocks stained clearly; some specimens were 22 years old. In several cases, tissues preserved in formalin for three years also stained well. The amount of beta granulation is easily determined. The acinar tissue stains a pale red to pink; the zymogen granules stain a very bright red. The beta cells show a dark blue granulation; the alpha cells a bright red granulation.

STAINING TECHNIC

Tissues which have been fixed in formalin for 24 hours or more are embedded in paraffin, sectioned at 5-8 micra, and affixed to slides in the usual fashion. The tissues on the slides are then mordanted overnight in a 16 per cent potassium chromate-4 per cent formalin solution. The following morning they are washed in tap water for a few minutes and then immersed in solution containing equal parts of a 0.3 per cent potassium permanganate and a 0.3 per cent sulphuric acid solution for five minutes. The potassium permanganate and sulphuric acid are mixed just before using.

The tissues are then put in a 2.5 per cent sodium bisulfite solution for five minutes, washed in tap water for ten minutes, and stained in chromium hematoxylin for 4-8 minutes. Staining in the chromium hematoxylin is done in the tissue oven at an elevated temperature (45°-55°C.). The tissues are then decolorized in 1 per cent acid alcohol for one minute, washed for one hour in tap water, and stained in 5 percent phloxin for 10 to 15 minutes. They are then rinsed in tap water, placed in 5 per cent phosphotungstic acid solution for one minute, and washed in tap water for ten minutes. The tissues are then carried through 95 per cent alcohol, two changes of absolute alcohol, three changes of xylol and coversliped with clarite or balsam.

The chromium hematoxylin stain is prepared as follows: Equal amounts of a 1 per cent aqueous hematoxylin solution and 3 per cent chrome alum solution are mixed. To 100 cc. of this solution are added 2 cc. of 5 per cent potassium bichromate and 2 cc. of 2.5 per cent sulphuric acid solution respectively. The stain should be allowed to ripen for a few days before using. It will give excellent results for at least one month and needs no special storing.

SUMMARY

A modification of Gomori's technic for the selective staining of islet cells has been described. It is a dependable stain for both human and animal pancreas and gives constant results. It is especially useful for the study of small biopsies of the pancreas.

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The Detection of Degenerative Diseases

In private practice the physicians can do far more in the prevention, retardation, and alleviation of disability that is due to chronic progressive disease in the aging and the aged than is being accomplished at present.[1] Aside from the instruction, guidance, and stimulation of motivation for effort toward the construction of optimum health by personal, tutor-like instruction,[2] the most important potentiality for service is the earliest possible detection of degenerative disease and the institution of measures to correct the known and/or suspected etiological factors. As previously pointed out, these disorders begin so silently and insidiously that they must be searched for if they are to be discovered in time to be amenable to therapy. To wait until obvious symptoms and signs appear is to wait too long. Irresversible damage is the price of procratination and lack of thoroughness in clinical study.

—From *"Chronic Illness and Senescence" by Edward J. Stieglitz, M.D.* in *The Journal* of the American Medical Association, October 4, 1952

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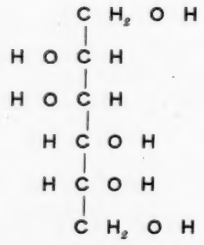
The Metabolism of Mannitol and Sorbitol

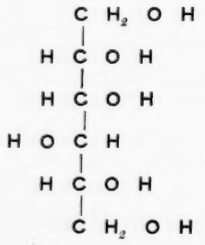
Their use as sugar substitutes in diabetic therapy

*William H. Olmsted, M.D.,** CHAIRMAN

The universal taste for sweet foods is the impetus for the search for sweeteners that may be used by diabetics. Glucose, fructose and sucrose are so rapidly absorbed that their use places a strain on the diabetic organism and they are avoided in the usual diabetic diet. Substitute sweeteners are of two classes, the chemical agents of which saccharine is the oldest representative and the hexahydric alcohols of which mannitol and sorbitol are best examples. This review is concerned with the metabolism of the latter in relation to their use by diabetics.



D Mannitol



D Sorbitol

Sorbitol is a white crystalline powder which is very soluble in water. It is a hydroscopic agent, a moisture conditioner widely used commercially to control the water content of a large number of manufactured products. In foods it is used to preserve the moisture content and texture and to impart a sweet taste. It is 60 per cent as sweet as sucrose. It was first recommended for use by diabetics in 1929 by Thannhauser in Germany. His suggestion stimulated discussion as to the suitability of sorbitol for use in diabetic diets; a discussion which is still active.

Mannitol is a white crystalline powder only 15 per cent soluble in cold water. It is the main constituent of manna, the solidified sap of a variety of ash found in southern Europe. It has been used for centuries as a mild cathartic. Since about 1940, when both mannitol and sorbitol were first made by an electrolytic reduction process from cornstarch or glucose, these alcohols have been available commercially at low cost. Mannitol is used in foods and pharmaceutical products as an inert powder filler. It is also useful in physiological studies. In 1940, Smith and others[19] showed that after injection intravenously, it is filtered by the renal glomeruli and not reabsorbed or excreted by the tubular epithelium. It also has been recommended for the determination of extracellular fluid volume. Both mannitol and sorbitol have been used by bacteriologists since the turn of the century in procedures for the identification of bacteria.

In the following discussion of the literature, no attempt has been made to record a complete bibliography. The important papers bearing on the physiology of these substances will be reported in some detail.

ABSORPTION

It long has been recognized that both mannitol and sorbitol are absorbed slowly from the gastro-intestinal tract of both animals and man. Carr and co-workers in 1933[3] and 1938[4] used a mixture of mannitol (one-third) and cacao-butter (two-thirds) to prevent diarrhea in experimental animals. When mannitol was given by stomach tube in a small amount (0.6 gm.) one-sixth was recovered from the intestine. In studying the nutritive value of mannitol and sorbitol in rats,

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Ellis and Krantz[12] fed a mixture of sugars consisting of 35 per cent glucose and only 5 per cent of one or the other of these alcohols, presumably because larger amounts would cause diarrhea. In man, these observers found the laxative dose of mannitol to be from 10 to 20 gm.

Blatherwick and others[2] gave 500 mg. of sorbitol to rats by tube, but the results of their experiments could be questioned because the animals had diarrhea. Ellis and Krantz[12] fed monkeys 2 gm. daily for 3 months and 10 gm. daily to 3 human subjects for 1 month without any evidence of toxicity (or, presumably, diarrhea).

Very recently experiments making use of glucose and sorbitol labeled with radioactive carbon (C^{14}) have appeared. Wick, Almen and Joseph[22] administered 300 mg. of glucose or sorbitol by stomach tube to female rats weighing 210 to 252 gm. Animals were sacrificed 1, 2 and 3 hours after ingestion of the test substance. The stomach and intestinal tract were removed and washed free of their contents. Absorption was calculated by the amount of radioactive material recovered from the intestinal contents. Glucose was absorbed rapidly, 97 per cent the first hour and 99 per cent by the third hour. In the case of sorbitol, on the other hand, 75 per cent was absorbed the first hour and 84 per cent by the end of three hours. The rate of absorption was further clearly demonstrated by tests of whole blood by Geiger counts made during absorption; glucose was absorbed 10 times more rapidly than sorbitol.

From the study of the literature one must distinguish between two different procedures used by experimenters. In one, the animal is starved for 48 hours and then fed by stomach tube an amount of the material to be studied; the animals being sacrificed at various times, from 1 hour to 12 hours. In such acute experiments it is difficult to demonstrate absorption. The other procedure is to incorporate the material in the diet in small amounts for several days. By this method, good evidence of its absorption can be obtained.

Eitel[10] long ago summarized the use of mannitol and sorbitol (along with many other carbohydrates) by fermentation procedures to identify bacteria, and more recently Dozois, Hochtel, Carr and Krantz[9] studied 127 strains of the colon-aerogenes groups of bacteria. All species produce acid and gas from cultures containing 1 per cent. Since mannitol and sorbitol in larger amounts escape absorption, they would be attacked by the bacterial populations of the lower gastro-intestinal tract with the production of the volatile fatty acids as shown by Grove, Olmsted and Koenig.[14] These acids stimulate the motility of the intestinal tract.[24] Mannitol and sorbitol also favor retention of fluid within the intestinal lumen.

METABOLISM

The metabolism of mannitol and sorbitol have been studied since 1933. Data is available bearing on the following effects: formation of glycogen both in the liver and muscles; appearance of hyperglycemia after feeding; elimination through the kidney, their usefulness in the study of kidney function, and for determination of extracellular fluid volume; effect on the respiratory quotient; antiketogenic agents; and, lastly, as agents to relieve insulin shock.

Mannitol: In 1933 Carr and others[3] fed mannitol mixed with cacao-butter to rats. The glycogen content of the livers was slightly, although significantly, increased over those of the controls. The respiratory quotient, however, was not significantly increased. When rabbits were given the alcohol by stomach tube, the blood sugar (glucose) rose slightly. In the same year Silberman and Lewis[17] gave mannitol by stomach tube to rats but found no significant rise in liver glycogen. Carr and Krantz[4] (1938) again fed a mannitol-cacao-butter mixture to rats and again found a liver glycogen content of 0.98 per cent compared to 0.18 per cent in controls. Glucose fed in the same amounts resulted in liver glycogen value of 3.14 per cent. In acute experiments when mannitol was given by stomach tube the effects were negative as in the experiments of Silberman and Lewis.

Todd, Myers and West[21] injected 22.5 gm. intravenously into dogs but found no increase in the true blood sugar. Mannitol was given by stomach tube or intraperitoneally but no rise in liver glycogen was detected. They repeated the feeding experiments in rats of Carr (one-third mannitol, two-thirds cacao-butter), and confirmed the latter's finding of increased liver glycogen (0.98 per cent); control (0.27 per cent). Ellis and Krantz[12] in Carr's laboratory (1941) reviewed the work on the sugar alcohols up to that time. They gave 9 gm. of mannitol per kg. by stomach tube to Macaca monkeys. Three hours later the liver glycogen had risen, much less so in case of mannitol than sorbitol. Mannitol was given to normal men and the respiratory quotient, as well as the true blood sugar, were determined at the end of ½, 1 and 2 hours. No significant influence either on true blood sugar or respiratory quotient was found. Johnston and Deuel[15]

(1943) using rats, studied the effects of mannitol, sorbitol and dextrose on muscle and liver glycogen and their antiketogenic effects in both exogenous and endogenous ketosis. The sugars were given intraperitoneally in two doses. They found mannitol to be antiketogenic, and therefore glucose forming, but only one-fourth as effective as glucose. As a glycogen former they found it only weakly active. In 1945 Carr and Krantz[6] again reviewed the literature on the metabolism of the sugar alcohols. They said: "To summarize, the fate of mannitol in the animal body appears to proceed along the following pattern: absorption from the alimentary tract; partial conversion to glycogen in the liver, and the elimination of much of the sugar alcohol unchanged in the urine."

In 1940 Smith and others[19] introduced mannitol as one of the substances that when given intravenously, is filtered through the glomeruli without being reabsorbed by the kidney tubules. In two human experiments 10 gm. of mannitol was given intravenously and, in 10½ hours, 81 and 89 per cent had been recovered in the urine. They reported that as much as 80 gm. of mannitol or sorbitol had been injected into human individuals. When sorbitol was injected intravenously in man, only 32 per cent was recovered in the urine. Dominguez, Corcoran and Page[8] studied mannitol as a measure of glomerular filtration and volume of extracellular fluid. They confirmed Smith's findings that 80 per cent of intravenously injected mannitol can be recovered in 10 hours. They concluded that it is metabolized at a very slow rate and that this rate could be expressed in mg. per minute per unit of plasma, a figure equalling 21 for human beings. Elkinton[11] studied mannitol as a measure of the volume of extracellular fluid. He injected 12 to 25 gm. of mannitol intravenously into three human subjects, two of them edematous. In an 8-hour collection of urine, he recovered from 89 to 99 per cent of injected mannitol. Clark and Barker[7] review their experience with mannitol injected to determine kidney function. In 90 unselected clearance periods in 29 tests on 22 patients, 100.4 mg. of mannitol were recovered for each 100 mg. injected. Therefore, they believe there is no extrarenal disposal of mannitol.

Sorbitol: After the introduction of sorbitol into the treatment of diabetes in 1929 much excellent work was done to reveal its metabolism. In Europe in the next few years, clinicians made claims both for and against its use in diabetic diets. Blatherwick and others[2] and Todd, Myers and West,[21] and later Ellis and Krantz,[13] who reviewed this controversy agreed that the reports were confusing. The particular interest in sorbitol is dependent on its better absorption, sweet taste and solubility.

Payne, Lawrence and McCance[16] (1933) fed 25 gm. of glucose, and at another time a like amount of sorbitol, to two juvenile diabetics. The blood sugar was determined at intervals up to 3 hours. After administration of sorbitol by mouth, the blood sugar values rose from 200 mg. per 100 cc. to 280 in one patient and from 83 to 120 in another. Sorbitol was added to the diet of diabetics and a reduction in acetone excretion was noted. Twenty gm. of sorbitol failed to relieve mild insulin hypoglycemia. Experimental animals (rats) on receiving sorbitol failed to show an increase in liver glycogen. From this observation the authors concluded that sorbitol could be safely used as a sweetening agent by diabetics. Silver and Reiner[18] fed 50 gm. of sorbitol to an individual with essential fructosuria and followed the glucose and fructose levels of the blood. Controls were a normal individual and a diabetic. In the case of the normal control there was no rise either in the blood or blood fructose. In the diabetic, the blood glucose rose from 180 to 260 mg. per 100 cc. in 3 hours. In the fructosuric patient, blood glucose did not rise but fructose values increased from 0 to 0.35 mg. per 100 cc. It was concluded that sorbitol may give rise to fructose. This observation is of particular interest in the light of the fact, later proved, that fructose is an intermediate product in the metabolism of sorbitol in the liver. Carr and Forman[5] (1939) fed to rats sorbitol and cacao-butter, in the manner previously referred to, and found the liver glycogen to be 1.25 gm. in contrast to 0.25 gm. in the controls.

They showed that sorbitol is not harmless, for if 2.6 gm. per 100 gm. of rat is fed, the rats died. Todd, Meyers and West[21] gave a 50 ml. of a 50 per cent solution of sorbitol intravenously to dogs; 39 per cent was recovered in the urine. Blood sorbitol and blood glucose levels were raised. The former returned to normal in 2 hours; the latter had returned to normal in one hour. They also found the liver glycogen increased after giving sorbitol by stomach tube to rats. Blatherwick and others,[2] however, after giving 500 mg. of sorbitol to rats found no increase in liver glycogen. Such an amount may be toxic (cathartic). Ellis and Krantz[12] (1941) obtained an increase in the liver glycogen of monkeys after giving 8 gm. per kg. by stomach tube. They further obtained an increase in the respiratory quotient of man, but no increase in blood sugar,

after giving sorbitol syrup by mouth. The same observers in 1943[13] gave 50 gm. of sorbitol by mouth to 13 diabetics and compared its effect on the blood sugar and respiratory quotient with 50 gm. of glucose. The averaged results revealed no rise either of the blood sugar level or of the respiratory quotient. In the case of glucose there was a great rise in blood sugar, as expected, but in addition a significant rise of the respiratory quotient.

Carr and Krantz[6] reviewing the metabolism of sorbitol say: "In the authors opinion, it (sorbitol) owes its value, in diabetes, to the fact that it is capable of being stored as glycogen and that its subsequent depolymerization and utilization fail to supply to the blood a plethora of glucose which would produce hyperglycemia." And further: - "Although the ingestion fails to produce a hyperglycemia, there can be no question about the presence of a sorbitolemia. The question, therefore, which remains unanswered is the relative effect on the impaired islet tissue of a hyperglycemia or a high blood-sorbitol level." Johnston and Deuel,[15] in experiments designed to test the glycogen production in both muscle and liver and the antiketogenic power of sorbitol in rats, came to these conclusions: Sorbitol is slightly *more effective* than glucose in causing deposition of liver glycogen when injected intraperitoneally. But, glucose acts more promptly in this respect. The ketolytic effect of sorbitol was only 50 per cent of that of glucose, in the case of exogenous ketonuria, and only 25 per cent of that of glucose when the ketonuria was of endogenous origin. The exogenous ketosis was produced by feeding sodium butyrate and the endogenous by feeding a high fat diet (Crisco). The liver, they concluded, converts sorbitol to glycogen, but in the case of extremely fatty livers, it fails to do so.

Stetten and Stetten[20] injected intraperitoneally into rats glucose and sorbitol made radioactive by the incorporation of C^{14} into the sugars. The animals were sacrificed at 6, 12, and 24 hours and the glycogen of both the liver and carcass was determined. The same procedure was applied to rats, made severely diabetic by alloxan. In addition the carbon dioxide of the expired air was collected and the urine was examined. With C^{14} labeled glucose and normal rats 50 to 60 per cent of the injected C^{14} found in the expired air and 11 to 13 per cent in the urine. When sorbitol was injected into normal rats, 64 per cent appeared in the expired air and 19 per cent in the urine; 0.7 percent of the liver glycogen contained C^{14} when glucose was injected; 0.12 per cent when sorbitol was given. These values for glycogen, which are low compared to other observations, were explained on the basis that the rats were not starved preceding injection. These observers concluded that sorbitol is metabolized as rapidly as glucose when injected intraperitoneally but is a poorer source of glycogen. They believed that fructose is an intermediate in the transformation of sorbitol to glucose. With diabetic rats, the sugars were largely excreted in the urine; in the case of glucose, 89 per cent and after sorbitol 78 per cent. Only small amounts appeared as labeled carbon dioxide, which was interpreted to mean that neither glucose or sorbitol had been metabolized.

Wick, Almen and Joseph[22] also used tagged glucose and sorbitol for administration by stomach tube or for intraperitoneal injection. Normal rats were used. The rate of oxidation was followed by the collection of the expired carbon dioxide every 3 hours up to 24 hours. Glucose by stomach tube or by injection gave almost identical rates of oxidation. In contrast the rate of oxidation for sorbitol was very much slower when the alcohol was administered by stomach tube. For instance, at the end of 3 hours, 11 per cent of sorbitol given orally had been oxidized, while 40 per cent was oxidized when sorbitol had been injected. When glucose was given, 55 per cent had been oxidized at the end of 3 hours. For the determination of glycogen, starved rats were used. In the case of both glucose and sorbitol, the livers contained 4.5 and 4.0 per cent respectively of glycogen. Of this amount, the authors calculated 40 per cent originated from the test substances. Equal amounts of tagged glycogen, but in small quantities, were recovered from the carcasses.

Blakely[1] studied the metabolism of sorbitol with liver slices and homogenates in the Warburg apparatus. As early as 1914, Embden and Guisbach had perfused the livers of phloridzinized dogs and concluded that sorbitol was oxidized to fructose and later transformed to glucose. Anschiel in 1930 had come to a like conclusion. Breusch (1942) had demonstrated sorbitol dehydrogenase in the brei of the liver of starved cats. Edson, using liver slices from starved cats, had found sorbitol more antiketogenic than glucose or fructose in rat livers. Blakely isolated in pure form the enzyme sorbitol dehydrogenase from the livers and kidneys of cats, mice, guinea pigs, and rabbits. Sorbitol dehydrogenase is specific and its action reversible:

Sorbitol$\rightleftarrows$fructose. Fructose$\rightarrow$fructose 6 phosphate. Fructose 6 phosphate$\rightleftarrows$glucose 6 phosphate. Glucose 6 phosphate$\rightarrow$glucose. Thus glycogen of liver is slowly

formed through fructose. This necessary series of enzyme phosphorylations takes some time and accounts for the delay observed by Johnston and Deuel for the formation of glycogen from sorbitol. Wick and Drury[23] have confirmed Blakely's findings by failing to find radioactive carbon in the expired air of eviscerated, nephrectomized rabbits.

SUMMARY

Mannitol is absorbed so slowly and to such a slight degree that it does not affect the blood sugar or respiratory quotient of man. What is absorbed would be eliminated in the urine to the extent of 80 per cent or more. The only positive evidence that mannitol enters the carbohydrate metabolism, is the small amount of glycogen found in the livers of starved rats fed mannitol for several days. Since only 10 to 20 gm. of mannitol can be fed to man without laxation, it does not appear to be of much importance as an adjunct to diabetic diets, and if used could probably be safely disregarded.

Sorbitol requires several hours for its absorption. In addition, a series of enzymatic phosphorylation reactions in the liver must take place to form glycogen from it. It does not raise the true blood glucose to any great degree. Given the time necessary for conversion, sorbitol is an excellent source of glycogen. In the diabetic rat, Stetten and Stetten found approximately as much sugar in the urine after sorbitol was injected intraperitoneally as after glucose. One would expect, therefore, that insulin would be required after sorbitol ingestion. However, since glucose formation from sorbitol is a delayed process, it may very well be that sorbitol might require less insulin than the rapidly absorbed glucose. Exact data on this point is not available. The literature would justify the classification of sorbitol as available carbohydrate and it should be calculated as such in diabetic diets.

How much sorbitol can be absorbed by man without the production of laxation? Ellis and Krantz fed 10 gm. of sorbitol to three human subjects for a month without ill effects. They found that 20 to 30 gm. of the commercial syrup was laxative but subjects could ingest 50 gm. of the crystalline product before laxation occurred. It is apparent, therefore, that the amount of sorbitol that can be absorbed is limited and that it cannot be considered a significant source of calories. One wonders whether sorbitol is not a physiological laxative agent in the sense that it is a substrate for the colonic bacterial population. Further, one wonders what effects it may have on bacterial metabolism and whether the result is favorable or unfavorable in human nutrition.

If sorbitol has a useful purpose in diabetic diets, it must be as an adjunct. As such it has two properties, that of a sweetener and as a moisture conditioner. In the former role it is but 60 per cent as sweet as glucose and is hardly a competitor of the chemical sweeteners. As a moisture conditioner it may be of considerable value. At this time one cannot predict what place sorbitol will occupy in diabetic diets and we must rely on the practical experiments of dietitians to solve that problem.

Finally, it seems highly important that foods containing sorbitol should be labeled in such a way as to show the amount of this substance present in the product.

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Experimentation in Human Beings

The Physician's Point of View

Present types of experimentation on the sick clearly challenge tremendously the basic concepts of the original patient-physician relationship. All the encroachments imposed by society upon this relationship, such as reporting certain diseases, requesting certain types of inoculations, evaluating fitness for work or right to compensation, shrink before the challenge the profession itself raises. . . .

Perhaps a glance at the way the legal profession meets the moral and technical demands of society and the individual when a conflict arises between the two will offer a cue to a solution of our problem. As we all know, that profession provides each of the two with a representative of equal stature: there, the prosecuting attorney, and here, the defense attorney. Similar arrangements may have to be developed in the field of human experimentation, performed not for the good of the individual patient but made to confirm or disprove or suggested biological generalization. Research and care would not be pursued by the same doctor for the same person, but would be kept distinct. The physician-friend and the physician-experimenter would be two different persons as far as a single patient is concerned—for instance, my patients would become research objects for someone else, and I would be permitted to experiment only with the patients of another physician. The responsibility for the patient as patient would rest, during the experimental period, with the physician-friend, unless the patient decided differently. Retaining his original physcian as personal adviser, the patient would at least be under less conflict than he is at present when the question of experimentation arises.

With reference to increasing technicalities, the forms that patients must sign when about to volunteer for experimentation, or even to undergo an operation might be so phrased as to state not only the patient's consent, but also the physician's affirmation of his utmost effort to protect the patient from harm and of his most careful judgement in deciding on an operation. Under those circumstances the obligations of the profession toward the individual and society would not be blurred.

The problem we face thus presents a true dilemma, being tragic in the classical sense; both its aspects are of equal value in thought, and a course of action must be decided anew for each actual situation, because the varieties of actual situations are as infinite as history itself. . . .

It is not the conquest of nature but the re-evaluation of man that appears to be the basic problems of our times. It is the re-evaluation of man as—to express it in old yet valid terms—"created in the image of God and tempted by the devil", not as a replica of innocent beasts, which, however cruel, cannot commit any crime. We must be alert with ourselves lest, in our zeal for the truth, we create healthy bodies at the cost of morally dulled minds.

From *Experimentation in Human Beings, The Physician's Point of View,* by Otto E. Guttentag, in Science *117*: 207-10, February 27, 1953

Recent Statistics On Diabetes

RECENT DATA ON DIABETES MORTALITY

Health conditions in the United States in 1952 were for the most part favorable and the death rate for the country fell to an all-time low, when allowance is made for the increase in the average age of the population. An important factor in the situation was the low prevalence of severe respiratory infection. This is reflected also in the decline in the mortality from diabetes in the country last year. Figures for the whole year are now available for the urban wage-earning population represented by the Industrial policyholders of the Metropolitan Life Insurance Company. They show that the death rate from diabetes dropped from 15.2 per 100,000 in 1951 to 14.0 last year, a reduction of 8 per cent.

Mortality data for the first three quarters of the year are available for the country as a whole, based on a 10 per cent sample, and for the several areas for which the statistics are collected.

The statistics for both the first six and first nine months of 1951 and 1952 are presented in Table 1. They indicate a modest decline in the death rate from diabetes in the country last year. In contrast, the rates in most of the large cities included in the table went up in varying degree. This holds true also for the two Canadian cities, Toronto and Montreal.

In England and Wales the death rate from diabetes in the first nine months of 1952 showed a sharp reduction as compared with the same period of 1951. The decline in mortality was 15 per cent, and was somewhat greater among men than among women. In great part, the improvement reflects the absence of any severe respiratory epidemic during the first nine months of last year, whereas in the early part of 1951 influenza was very prevalent and caused a sharp though temporary rise in the death rate from several diseases including diabetes. If comparison is made with the years prior to 1949, it is found that the death rate from diabetes in England and Wales is below that for any similar period in recent years except 1948.

Figures for the broad geographic divisions of this country, based upon the 10 per cent sample, are shown in Table 2. For most areas of the country the death rates in both the first half and the first nine months of last year were lower than in the two preceding years. For the first nine months the rise over 1951 was particularly marked in the Middle Atlantic and Mountain regions. The rate for the latter, however, is based on a relatively small number of deaths and is subject to wide fluctuation.

DIABETES AND OVERWEIGHT

The association between overweight and diabetes is certainly well established. Nevertheless, up-to-date statistics on the matter have interest and value for physicians. New data are available on the mortality from diabetes in a follow-up study of approximately 51,000 policyholders of the Metropolitan Life Insurance Company who were rated up solely because of overweight. The study was based upon those insured between 1925 and 1934 and traced to 1950. Thus the period of observation extends up to 25 years. Table 3 presents the facts on the excess mortality of these over-weight persons from a number of diseases. It is significant that the relative excess of the death rate from diabetes, is greater than for any other major disease. Among males the death rate from diabetes was nearly four times that among standard risks, and for females the ratio was about of the same order. This may be compared with a ratio of approximately 1½ times the expected for all causes in overweights of both sexes.

Submitted by Herbert H. Marks, Chairman, Committee on Statistics. The Committee welcomes suggestions or actual material suitable for these papers from Association members and other readers of the Journal.

CAUSES OF DEATH AMONG DIABETICS AND DURATION OF DIABETES IN FATAL CASES

The proportion of deaths from arteriosclerosis among diabetics steadily mounts as the mortality from infec-

(*Continued on page* 141)

TABLE 1. RECENT DATA ON DIABETES MORTALITY

Deaths and Death Rates—January-June and January-September 1951 and 1952

Area	Death Rates per 100,000 Jan.-Sept. 1952	Jan.-Sept. 1951	Jan.-June 1952	Jan.-June 1951	Number of Deaths Jan.-Sept. 1952	Jan.-Sept. 1951	Jan.-June 1952	Jan.-June 1951
United States (10% sample)	16.2	16.4	16.6	17.0	1,877	1,881	1,276	1,288
Metropolitan Life Ins. Co.								
Industrial Policyholders	14.0	15.2	14.3	16.5	1,949	2,127	1,325	1,539
New York State	20.7	20.0	21.2	21.1	2,361	2,248	1,612	1,579
New York City	20.5	19.5	20.7	20.4	1,235	1,159	835	808
Maryland, Resident	19.2	20.0	20.1	22.4	351	359	245	267
Baltimore	24.3	21.6	24.0	24.3	174	154	114	102
Boston	25.0	25.3	28.6	23.6	150	153	114	94
Philadelphia	27.0	24.9	29.2	27.0	426	389	307	280
Toronto	16.2	15.7	15.1	16.3	81	77	50	53
Montreal, Resident	17.3	15.8	17.0	17.6	134	121	88	90
London (Administrative County)					219	241	156	169
England and Wales								
Total	7.4	8.7	8.2	9.7	2,442	2,840	1,776	2,100
Males	5.0	6.0	5.6	6.7	795	938	589	702
Females	9.6	11.2	10.5	12.4	1,647	1,902	1,187	1,398

Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 percent sample of death certificates received in vital statistics offices, as published in Current Mortality Analysis, a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2 NUMBER OF DEATHS AND DEATH RATES FOR DIABETES IN GEOGRAPHIC DIVISION United States Reporting Area for the 10-percent Sample; First Six Months and First Nine Months 1950, 1951 and 1952

Geographic Division	Death Rates per 100,000* 1952	1951	1950	Number of Deaths* 1952	1951	1950
			January-September			
U. S. reporting area	16.2	16.4	16.5	1877	1881	1859
New England	20.0	25.4	21.2	142	170	147
Middle Atlantic	22.0	18.1	20.8	510	415	476
East North Central	19.5	20.8	21.2	458	480	485
West North Central	17.7	18.2	17.5	192	195	187
South Atlantic	11.8	13.0	13.8	193	209	210
East South Central	9.9	10.6	9.4	87	93	80
West South Central	9.9	13.1	10.7	111	145	117
Mountain	15.5	10.1	7.8	61	39	28
Pacific	11.2	12.3	11.6	123	135	129
			January-June			
U. S. reporting area	16.6	17.0	17.4	1276	1288	1299
New England	20.9	26.4	21.1	98	119	98
Middle Atlantic	23.1	18.3	22.5	356	278	341
East North Central	20.8	22.2	22.2	324	339	337
West North Central	17.5	20.3	19.0	126	144	135
South Atlantic	11.7	13.1	15 2	127	140	153
East South Central	10.7	9.9	8.3	63	57	47
West South Central	9.3	12.2	11.6	69	89	84
Mountain	14.6	11.7	8.5	38	30	20
Pacific	10.4	12.6	11.5	75	92	84

*Excludes armed forces overseas.

Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 3 PRINCIPAL CAUSES OF DEATH AMONG MEN AND WOMEN LIMITED TO SUBSTANDARD INSURANCE BECAUSE OF OVERWEIGHT, ATTAINED AGES 25-74 YEARS.

Issues of 1925-1934 Traced to Policy Anniversary in 1950
Metropolitan Life Insurance Company

Death Rates of Standard Risks in Each Sex = 100 Percent

Cause of Death	Men Number of Deaths	Men Per cent Actual of Expected Deaths	Women Number of Deaths	Women Per cent Actual of Expected Deaths
All Causes*	3,713	150	2,687	147
Diabetes mellitus	205	383	235	372
Principal cardiovascular-renal diseases	1,867	149	1,103	177
Organic heart disease, diseases of the coronary arteries and angina pectoris	1,377	142	697	175
Cerebral hemorrhage	247	159	226	162
Chronic nephritis	243	191	180	212
Cancer—all forms	385	97	476	**100**
Leukemia and Hodgkin's disease	26	**100**	23	**110**
Tuberculosis—all forms	24	21	20	35
Pneumonia—all forms	98	**102**	78	**129**
Cirrhosis of the liver	96	249	32	**147**
Appendicitis	76	223	41	195
Biliary calculi (gallstones)	19	206	50	284
Ulcers of stomach and duodenum	30	67	10	**

*All ages, 20 and over.

** Deaths too few to warrant calculation of mortality ratio.

Note: Boldface denote that the deviation from the Standard is not statistically significant.

TABLE 4 PRINCIPAL CAUSES OF DEATH OF 12,281 DIABETICS

Experience of Joslin Clinic, Boston, Mass. 1898-1951*

Cause of Death	Naunyn Era 1898 to May 31, 1914	Allen Era June 1, 1914 to Aug. 6, 1922	Banting Era Aug. 7, 1922 to Dec. 31, 1936	Hagedorn Era Jan. 1, 1937 to Dec. 31, 1943	Chas. H. Best Era Jan. 1, 1944 to April 27, 1951
	Per cent of All Causes				
All Causes	100.0	100.0	100.0	100.0	100.0
Diabetic coma (primary)	63.8	41.5	8.3	2.9	1.8
Cardio-renal-vascular	17.5	24.6	54.4	65.7	70.8
Arteriosclerotic	17.5	24.3	54.0	65.3	70.2
a. Cardiac	6.1	9.9	29.8	41.3	46.5
b. Nephritic	3.4	3.8	4.8	4.6	6.7
c. Apoplexy	2.8	4.9	9.3	11.6	12.3
d. Gangrene	3.7	4.2	8.0	5.2	2.8
e. Site unassigned	1.5	1.4	2.1	2.6	1.8
Other circulatory and rheumatic heart disease	—	0.4	0.4	0.4	0.6
Infections, total	7.4	12.7	13.6	10.4	6.6
Pneumonia & respiratory	4.3	7.7	6.8	5.6	4.1
Gall-bladder	—	0.5	0.5	0.5	0.3
Carbuncle	1.8	1.6	1.0	0.5	—
Kidney, acute	—	0.1	0.9	0.9	0.8
Other infections	1.2	2.8	4.4	2.8	1.3
Cancer	1.5	3.8	8.7	8.7	9.2
Tuberculosis	4.9	4.9	4.1	2.3	1.9
Accidents	—	0.8	2.1	1.8	2.1
Inanition	0.3	2.2	0.1	—	**
Insulin reactions	—	—	0.2	0.3	0.3
All other and unknown causes	4.6	9.4	8.5	7.9	7.4
Number of deaths	326	836	4138	3482	3499

*Deaths reported through April 27, 1951.
**Less than .05.

TABLE 5 PRINCIPAL CAUSES OF DEATH OF 656 DIABETICS

Deaths Between January 1, 1950 and 1952*
Experience of Joslin Clinic, Boston, Mass.

Cause of Death	Per cent of All Causes
All Causes	100.0
Diabetic Coma (Primary)	1.1
Cardio-renal-vascular	75.9
Arteriosclerotic	75.6
Cardiac	47.6
Coronary and Angina	35.8
Renal, total	13.0
Diabetic Nephropathy	9.3
Typical or Unqualified**	8.2
Probable	1.1
Cerebral	12.7
Gangrene	1.1
Site Unassigned	1.4
Other circulatory and rheumatic heart disease	0.3
Infections, total	5.8
Pneumonia and respiratory	4.0
Gall bladder	0.2
Kidney, acute	0.6
Other infections	1.2
Cancer	9.6
Tuberculosis	0.9
Accidents	1.8
Insulin reactions	0.2
All Other and unknown causes	4.8
Number of deaths	656

*Deaths reported through April 7, 1952
**22 confirmed by autopsy

TABLE 6 DIABETES MORTALITY AMONG 656 DECEASED DIABETICS

Deaths Between January 1, 1950 and 1952*
Experience of Joslin Clinic, Boston, Mass.

a. Average Duration of Life Subsequent to Onset of Diabetes, By Age Groups at Onset

Age Groups at onset	Number of cases	Duration years
All Ages	656	15.2
0-9	27	21.2
10-19	52	19.3
20-39	102	21.1
40-59	314	15.5
60 & over	161	8.5

b. Duration of Life Subsequent to Onset of Diabetes: Number and Percent of Cases Classified According to Duration

Duration years	Number of cases	Percent
All Cases	656	100.0
Less than 5	88	13.4
Less than 1	18	2.7
1	19	2.9
2	20	3.0
3	18	2.7
4	13	2.0
5-9	107	16.3
5	16	2.4
6	24	3.7
7	20	3.0
8	15	2.3
9	32	4.9
10-14	146	22.3
15-19	120	18.3
20 & over	195	29.7
Average 15.2	Median 14.5	

*Deaths reported through April 7, 1952.

(*Continued from page* 138)

tions and diabetic coma declines. As Table 4 shows, 7 out of 10 deaths among patients of the Joslin Clinic since 1944 have been due to arteriosclerosis in its various manifestations. This compares with approximately two thirds of the deaths in 1937-1943 and a little over half in the period 1922-1936. The only major category in the arteriosclerosis group to show a decrease is gangrene, which in the latest period accounted for less than 3 per cent of the deaths as compared with 5.2 per cent in 1937-1943. Cancer ranks next to arteriosclerosis among the causes of death in this experience, with 9.2 per cent of all deaths since 1944 as compared with 6.6 per cent for infections as a group.

The facts on the causes of death in the experience of the Joslin Clinic between January 1, 1950 and April 7, 1952 include a more detailed statement with regard to renal deaths, and in the light of recent developments, special attention has been paid to diabetic nephropathy. Of the 656 deaths recorded in the period specified, 3 out of 4 were due to arteriosclerosis. Of the total, 13 per cent are ascribed to renal causes, including 9.3 per cent specified as nephropathy. In the majority of these cases the available details supported this diagnosis, with confirmatory evidence from autopsy in 22 of the 61 cases classified as nephropathy. In this recent series, only 1.1 per cent of the deaths was due to primary diabetic coma. These data are presented in Table 5.

Facts on the duration from onset to death for the fatal cases from 1950 to April 7, 1952 are shown in Table 6. For all cases the average duration was 15.2 years; for cases with age at onset under 40 it was at its maximum, exceeding 21 years, for the age groups under 10 and 20 to 39.

Among these 656 recent fatal cases only 2.7 per cent of the deaths occurred within a year after onset and only 13.4 per cent within five years of onset. In nearly one third of the cases the duration exceeded 20 years.

Physical Medicine and Obesity

Insofar as reduction of weight is concerned, physical agents are capable only of increasing the caloric output or the fluid output of the human body and they are not capable of diminishing caloric input. Because any increase of output of fluids must promptly be compensated for by an equal input of fluids and because increasing the caloric output is extremely difficult and often dangerous, the limitations of physical medicine in reducing bodily weight immediately became apparent.

Many nonmedical "weight-reducing parlors" or "slenderizing salons" exploit various combinations of baths, massage and exercise. Usually such plans for reduction of weight depend basically on a special low-calorie diet which is introduced somewhat surrepitiously in conjunction with the highly tooted physical procedures. . . .

All of the hot baths can produce a transient loss in weight through the production of profuse perspiration. Loss of weight from sweating may exceed 2 pounds in an hour when a patient is placed in any one of these hot baths. However, such reduction in weight by loss of water from the tissues does not indicate that there has been decrease in the amount of adipose tissue and the body will soon regain enough water to make up for this transient dehydration. . .

Stimulating cold baths, Scotch douches and needle showers produce a mild increase in tone of muscles with a slight increase in metabolic rate. Although they produce a feeling of well-being, the increase in metabolic rate is so slight and of such short duration that it is not sufficient to produce any noticeable loss of weight.

Strangely, it does not seem to be well known, even among members of the medical profession, that no form of external manipulation is capable of removing adipose tissue from a particular region of the body. Massage will not reduce local deposits of fat. Massage will not increase muscular strength. Massage will not cause any significant change in the basal metabolic rate. . .
There is no scientific proof whatever that massage of any type can be effective as a reducing measure.

—From *Physical Medicine and Obesity* by Frank H. Krusen, M.D. in *The Journal* of the American Medical Association

ABSTRACTS

Abraham, S.; Chaikoff, I. L.; and Hassid, W. Z. (*Div. of Physiol., Sch. of Med., and Div. of Plant Biochem., Coll. of Agriculture, Univ. of California, Berkeley*): CONVERSION OF C^{14} PALMITIC ACID TO GLUCOSE. II. SPECIFIC GLUCOSE CARBONS LABELED. J. Biol. Chem *195*:567-81, April 1952.

The investigation deals with the conversion of a naturally occurring, long-chain fatty acid, palmitic, to urinary glucose in the totally depancreatized dog. The incorporation of the isotopically labeled carboxyl carbon, palmitic acid-1-C^{14}, and the 6th carbon, palmitic acid-6-C^{14}, into the various carbon atoms of the glucose molecule is reported. In order to obtain the C^{14} content of individual carbon atoms of glucose, a new procedure for the degradation of the glucose molecule was developed. C^{14}-labeled, chromatographically pure, crystalline glucose was isolated from the urine of diabetic dogs that received either palmitic acid-1-C^{14} or palmitic acid-6-C^{14}. About 6 per cent of the carboxyl carbon was recovered as urinary glucose in 48 hours, and about 14 percent of the 6th carbon in 96 hours. In the experiment with palmitic acid-1-C^{14}, all the C^{14} activity was found in carbons 3 and 4 of the isolated urinary glucose. The C^{14} activity was equally distributed between these two carbons. When palmitic acid-6-C^{14} was administered, about 10 per cent of the C^{14} activity resided in each of carbons 3 and 4 of the isolated urinary glucose. The remaining 80 per cent of the C^{14} was equally distributed among carbons 1, 2, 5, and 6. In the light of such labeling, the authors discuss the pathway of conversion of long-chain fatty acids to glucose.

Adams, Adrian V. (*Heathfield, Sussex, England*): CORRESPONDENCE: TUBULAR REABSORPTION OF GLUCOSE. Brit. M. J. 2:993, November 1, 1952.

The author discusses, in a letter, a recent paper on renal physiology by P. Govaerts (July 26, p. 175). The problem under discussion is why the tubular mechanism does not work really efficiently unless liberal quantities of glucose reach it through the glomeruli. No explanation is offered.

Altschule, M. D.; Parkhurst, B. H.; and Owens, M. G. (*Lab. of Clin. Physiol. McLean Hosp., Waverley, Mass., and Dept. of Med., Harvard Med. Sch., Boston*): CHANGES IN GLUCOSE TOLERANCE AS AN INDEX OF IMPROVEMENT AFTER ELECTROSHOCK THERAPY. Proc. Soc. Exper. Biol. & Med. 80:436-39, July 1952.

The effect of electroshock therapy on glucose metabolism was studied in 12 psychotic patients who improved under this treatment. Changes in sugar tolerance varied in direction and degree; there was no correlations with clinical improvement.

Annotations (*England*): ACTION OF INSULIN ON THE LIVER. Lancet 2:817, October 25, 1952.

The apparently differing effect of insulin on the liver of normal and of diabetic animals has long been a puzzle. In diabetic animals, formation of liver glycogen seems to be increased by insulin, whereas in normal animals it seems to be decreased. Macleod drew attention to this anomaly in 1934. Soskin suggested that any insulin administered to the normal animal was an excess over the optimal amount already present and caused hypoglycemia; this in turn brought into operation a compensatory hepatic glycogenolysis. The adrenalin mechanism very probably mediates this glycogenolysis in the liver, since removal or denervation of the adrenal glands prevents a depletion of liver glycogen following hypoglycemia. In some experiments with perfused livers, however, in which hepatic glycogenolysis followed the administration of insulin, adrenalin played no part. In these experiments, only certain samples of insulin showed glycogenolytic effects, although all were thera-

peutically active. Bridge even demonstrated depletion of hepatic glycogen after injection of insulin into normal animals which were protected from hypoglycemia by glucose infusions or which had been previously adrenalectomized, but he used a brand of insulin later shown by de Duve and others to contain the glycogenolytic factor, glucagon. Bouckaert and de Duve reinterpreted Bridge's results in the light of this knowledge and concluded that with glucogon-free preparations of insulin, Bridge would have observed an increase in hepatic glycogen proportionate to the dose of insulin, provided that the blood-sugar had been kept fairly normal by regulating the glucose infusion. Work by the Louvain school has confirmed the relative preponderance of the hepatic action of insulin over its peripheral action—a theme previously developed by Soskin. With small doses of insulin the ration of hepatic action to peripheral action is up to 2 to 1, but with very heavy doses it reaches 8 to 1 in favor of the liver. This predominant localization of the action of insulin in the liver is further illustrated by recent isotope studies on lipogenesis in the liver of the rat. Chernick and Chaikoff, using glucose labeled with C^{14}, have shown that insulin stimulates the incorporation of glucose into glycogen, carbon dioxide, and fatty acids, the stimulation of lipogenesis exceeding that of carbon-dioxide formation. It is thus possible that glycogenolysis in the normal liver after the administration of insulin does not necessarily represent increased glucose production but may be due, at least partly, to increased formation of fatty acids.

Sherlock and her collaborators, who have studied "normal" and diabetic patients by hepatic-vein catheterization, conclude that the liver is largely, but not wholly, responsible for the fall in the blood-sugar level after an injection of insulin. In normal persons there was a correlation between the diminished hepatic output and increased peripheral utilization of glucose; this was not apparent in diabetics, however, in whom two types of response could be distinguished. In one group, corresponding to the elderly obese diabetic often with cardiovascular complications, the effect of insulin was mainly an increase in peripheral utilization of glucose but with a relatively slight fall in blood sugar. The other group—the young, thin diabetic with minimal complications—responded to insulin by a large drop in the capillary glucose level, mainly due to diminished hepatic production. Aspiration biopsy of the liver showed normal liver cells in the hepatic-sensitive group and fatty change in the hepatic-insensitive group.

It now seems possible to have a unitary conception of the action of insulin in normals and diabetics; for insulin has been shown consistently to stimulate formation of liver glycogen, if freed from the opposing effects of hypoglycemia with release of adrenalin and of contaminating glucagon derived from the pancreatic *a* cells.

Annotations (*England*): INSULIN SUPPLY. Lancet 2:924, November 8, 1952.

The author discusses a recent inquiry by the British courts into the manufacture and distribution of insulin in the United Kingdom. The Monopolies Commission was unable to criticize the character of the various manufacturers.

Annotations (*England*): PERSPECTIVE OF DIABETES. Lancet 2:1073, November 29, 1952.

Editorial comment is made concerning the wide experience of the Joslin group in the study and treatment of diabetes and the value of the new edition of Dr. Joslin's monumental contribution, *Treatment of Diabetes Mellitus.*

Ashworth, M. A.; Kerbel, N. C.; and Haist, R. E. (*Dept. of Physiol., Univ. of Toronto, Toronto, Canada*): EFFECT OF CHRONIC CALORIC INSUFFICIENCY ON THE GROWTH OF THE ISLETS OF LANGERHANS. Am. J. Physiol. *171*:25-28, October 1952.

Undernutrition just sufficient to maintain the initial body weight in young rats prevents the growth of the islets of Langerhans. This leads to a significant difference in islet weights between the undernourished rats and controls fed ad libitum. Under these conditions of undernutrition the pancreas weight increases, even though the body weight does not. In order just to maintain the body weight in the fourth week, a smaller amount of food is required than in the first week of the undernutrition period.

Audy, Genevieve; and Kerly, Margaret (*Dept. of Biochem., Univ. Coll., London*): THE CONTENT OF GLYCOGENOLYTIC FACTOR IN SOME INSULIN SAMPLES. Biochem. J. 52:70-74, September 1952.

Two methods have been used for the assay of glycogenolytic factor in insulin samples. The first, or single-

dose, method allows rapid testing of samples and gives an approximate estimate of activity; the second, or multiple-dose, method requires testing at several concentrations and statistical treatment of results. Twenty-three commercial insulin samples have been assayed. The glycogenolytic factor content was found to vary considerably; no samples were found to have a higher activity than the sample used as a standard (prepared by Eli Lilly and Company and received in 1947). Several were free from glycogenolytic factor.

Azerad, E.; Lestradet, H.; and Alagille, D. (*Paris*): A STUDY OF DIABETIC KETOSIS AND ACIDO-KETOSIS. II. COMMENTS ON TWO CASES OF DIABETIC COMA (SEVERE DIABETIC ACIDO-KETOSIS). La presse Médicale 60:1702-05, December 17, 1952.

The authors report two cases of severe diabetic acidoketosis evidenced by a very marked reduction in blood *p*H, the presence of a high ketonemia, high glycemia, and a more or less profound impairment of consciousness. They think that, therapeutically, the correction of acidosis (namely, the return to a normal blood *p*H) should be a preliminary phase in the course of treatment, since it may by itself restore the enzymatic and insulin activity, improve the cellular, and cerebral metabolism, and control, at least partially, the vascular disorders. All of these conditions are manifested by an improvement and even a clinically apparent cure. However, such a control of acidosis should be cautiously carried out in order to avert secondary alkalosis.

Aziz, Sedki; and Bebawi, Ernest (*Kasr el Aini Hospital, Cairo, Egypt*): THE INSULIN TOLERANCE TEST IN PITUITARY AND THYROID DISEASE. J. Roy. Egyptian M. A. 35:627-33, 1952.

Twelve patients with pituitary or thyroid disease were investigated regarding their response to intravenous injection of insulin. The insulin tolerance test was found to be normal in all except two cases. In one case of panhypopituitarism there was hypoglycemic unresponsiveness, with slowed return to normal blood sugar levels; in a case of cretinism, the patient was found to be resistant to insulin.

Berk, Edward J.; and Krumperman, LeRoy W. (*Depts. of Med. and Anesth. and the Fels Res. Inst., Temple Univ., Philadelphia*): THE USE OF FRACTIONAL EPIDURAL BLOCK IN THE MANAGEMENT OF ACUTE PANCREATITIS. Am. J. M. Sc. 224:507-13, November 1952.

Fractional epidural block is a valuable but not invariably effective means of controlling pain in severe acute pancreatitis. Even when it succeeds in abolishing pain, this procedure does not appear to alter the disease process itself. Fractional epidural block should be considered a useful adjunct to but not a substitute for other therapeutic measures in severe pancreatitis.

Bickel, H.: and Hickmans, Evelyn M. (*Dept. of Pediatrics and Child Health, Univ. of Birmingham, and Children's Hosp., Birmingham*): PAPER CHROMATOGRAPHIC INVESTIGATIONS ON THE URINE OF PATIENTS R. T. AND R. R. Arch. Dis. Childhood 27:348-50, August 1952.

Paper chromatographic studies on two patients suffering from galactosemia revealed, besides galactose, a pathologic excretion of various aminoacids in the urine. Galactosuria was demonstrated by chromatography even where the galactose concentration was too weak for a positive Benedict test. The aminoaciduria persisted after cessation of the galactosuria following a galactose-free diet. The pattern of the aminoaciduria was similar to that in other cases of liver damage. A kidney lesion as a possible cause of the aminoaciduria however, also has to be taken into account. Future investigations into the plasma level of the various aminoacids may reveal the mechanism of the aminoaciduria.

Birge, Henry L. (*Associate Ophthalmologist, Hartford Hosp. Asst. Clin. Prof. of Ophthalmology, Yale Sch. of Med.*): NEW THEORIES OF RETINAL VENOUS THROMBOSIS. Connecticut M. J. 16:582-86, August 1952.

Possible etiologic factors in retinal venous thrombosis include infection (direct or focal), neoplasm, surgery (rare), cardiac decompensation, trauma, arteriosclerosis, diabetes, hypertension, glaucoma and polycythemia. Many of the cases the author saw were associated with venous engorgement and cyanosis in the unaffected eye.

"Blood volume" estimations revealed that many of the cases showed mild degrees of polycythemia. Mild degrees of polycythemia exist more frequently than were formerly recognized, and it is believed that the polycythemia predisposes these patients to retinal (as

well as other) thromboses. Cases complicated by diabetes have all been more serious.

Blood study should include the "blood volume" as well as a search for abnormal blood cells. Blood sugar and uric acid should also be determined.

The fact that 56 per cent of polycythemics die from either hemorrhage or thrombosis makes it probable that a higher percentage of minor hemorrhages and thromboses (ocular) have a polycythemic etiology. The author's ten cases were treated only with phlebotomy. Phlebotomy to produce normal blood volume may be repeated whenever necessary every six weeks, if required.

Book Review (*England*): DIABETES AND PREGNANCY. Lancet 2:968, November 15, 1952.

A new book entitled *Blood Sugar of Newborn Infants during Fasting and Glucose Administration,* by Jorgen Pedersen, is reviewed.

Busch, Harris; and Potter, Van R. (*McArdle Mem. Lab., Med. Sch., Univ. of Wisconsin, Madison*): MULTIPLE EFFECTS OF FLUOROACETATE ON PYRUVATE METABOLISM IN VITRO. Proc. Soc. Exper. Biol. & Med. 80:701-04, August-September 1952.

Citrate formation is increased and oxidation is diminished by addition of fluoroacetate to rat kidney homogenates; under the same conditions, citrate formation is decreased, acetoacetate formation is increased, and oxidation is unchanged in liver homogenates. At higher concentrations of fluoroacetate, acetoacetate formation is also inhibited in liver homogenates.

Campbell, P. N.; and Young, F. G. (*Dept. of Biochemistry, Univ. Coll., London, W.C. 1*): METABOLIC STUDIES WITH 3-METHYL GLUCOSE. I. ITS FATE IN THE ANIMAL BODY. Biochem. J. 52:439-44, November 1952.

The administration of a solution of 3-methyl glucose to normal rats did not lead to a significant increase in the glycogen content of the liver or carcass or to the formation of any significant amount of monomethyl glycogen in the liver or carcass. No significant increase in the amount of volatile reducing substances in the urine took place after the administration of 3-methyl glucose to the rat, but a reducing sugar shown to be unchanged 3-methyl glucose was excreted. An average recovery in the urine of 92 per cent of the administered sugar was obtained after an intraperitoneal injection of 3-methyl glucose to the rat.

Carreras, M. A. (*Tucson, Ariz.*): DIABETIC ACIDOSIS. Southwestern Med. 33:438-41, December 1952.

A discussion of the physiology and treatment of diabetic acidosis.

Chaikoff, I. L.; and Tomkins, G. M. (*Div. of Physiol., Univ. of California Sch. of Med., Berkeley*): CHOLESTEROL SYNTHESIS BY LIVER. I. INFLUENCE OF FASTING AND OF DIET. J. Biol. Chem. 196:569-73, June 1952.

The authors investigated the effect of nutritional state of the rat upon the capacity of its liver to synthesize cholesterol from acetate labeled with radioactive carbon (C^{14}). They found that fasting for 24 hours or longer reduced the liver's ability to incorporate acetate carbon into cholesterol. Caloric restriction for several days also reduced the liver's ability to form cholesterol. The administration of glucose or a protein hydrolysate or fat restored cholesterol synthesis to normal in the fasted rat's liver.

Child, Charles, G. III; and Payne, Mary Ann. (*Dept. of Surg. and Med., New York Hosp., Cornell Med. Center, New York City*): HEPATIC PHYSIOLOGY AND THE SURGICAL PATIENT. S. Clin. North America 32:599-615, 1952.

The authors present a detailed discussion of the liver in relation to the effects of anesthesia and drugs, the nutrition of the surgical patient, diagnostic studies and therapy.

Cooper, David A.; and Boucot, Katharine. (*Sch. of Med., Univ. of Pennsylvania, and Woman's Med. Coll., Philadelphia*): TUBERCULOSIS AND DIABETES. Am. J. Nursing 52:1338-39, November 1952.

Tuberculosis is a special hazard to the person who has a severe form of diabetes, particularly to the diabetic who is under forty. Some workers believe that the in-

creased susceptibility of the diabetic to tuberculosis is due to a disturbance of protein and fat metabolism. Hemoptysis tends to be more frequent among tuberculous diabetics. Mortality from tuberculosis is falling among diabetics just as it is among nondiabetics. Unfortunately, morbidity remains high; therefore, it is fallacious to view the problem through mortality statistics alone.

Craig, J. W.; Drucker, W. R.; Miller, Max; Owens, J. E.; Brofman, B.; Pritchard, W. H.; and Woodward, H., Jr. (*Cleveland*): METABOLISM OF FRUCTOSE IN THE LIVER OF NORMAL AND DIABETIC SUBJECTS. Am. J. Med. *12*:610, May 1952.

Hepatic-vein catheterization studies were performed in two diabetic and three normal subjects. Hepatic venous and femoral arterial bloods obtained before, during, and following intravenous administration of fructose (1 gm. per Kg.) were analyzed for fructose, glucose, and pyruvic, lactic, citric, and malic acids. With the bromsulphthalein method being used for estimation of the hepatic blood flow, net splanchnic assimilations were calculated. The response to fructose of the diabetic patient deprived of insulin was found to be similar to that of the normal subject. The liver rapidly removed fructose from the blood; approximately half of the administered fructose was taken up by the liver during the period of administration. The authors conclude from these studies that (1) the liver plays an important role in the removal of fructose from the blood and converts a significant quantity to pyruvate, presumably by way of the Embden-Meyerhof scheme and, (2) the liver of the diabetic subject, in the absence of insulin, metabolizes fructose in the same manner as does the liver of the normal individual.

Cummins, Alvin J. (*Dept. of Med. ,New York Hosp.-Cornell Med. Center, New York City*): ABSORPTION OF GLUCOSE AND METHIONINE FROM THE HUMAN INTESTINE; THE INFLUENCE OF THE GLUCOSE CONCENTRATION IN THE BLOOD AND IN THE INTESTINAL LUMEN. J. Clin. Investigation *31*:928-37, October 1952.

An evaluation of the Nicholson-Chornock procedure for the study of human small bowel absorption is reported. The evaluation is based on use of the procedure in eighteen subjects for the study of glucose and methionine absorption. The technique appears to be of definite value in the investigation of certain aspects of absorption but has serveral sources of error which limit its usefulness.

Within the limits of sensitivity of the procedure, no detectable influence on the absorption rate of glucose or methionine could be demonstrated by elevating the blood sugar with intravenous glucose or by reducing it with insulin.

Daeschner, C. W. (*Dept. of Pediat., Baylor Univ. Coll. of Med., Dallas*): A BRIGHTER OUTLOOK FOR THE JUVENILE DIABETIC PATIENT. Texas State J. Med. *48*:694-97, October 1952.

Early onset of degenerative vascular disease uniformly occurs in the poorly regulated diabetic patient. Providing the best possible program of regulation is the physician's obligation. The program includes avoidance of emotional factors, prevention of progressive tuberculosis, intelligent management of intercurrent acidosis, and the maintenance of blood sugar values as near the normal range as is consistent with a relatively normal and useful life.

De Bodo, R. C.; Sinkoff, M. W.; and Kiang, S. P. (*Dept. of Pharmacol., New York Univ. Coll. of Med., New York City*): COMPARISON OF INSULIN HYPERSENSITIVITY OF ADRENALECTOMIZED AND OF HYPOPHYSECTOMIZED DOGS. Proc. Soc. Exper. Biol & Med. *80*:350-54, June 1952.

The adrenalectomized dog is more sensitive to insulin than the normal dog but less sensitive than the hypophysectomized dog. This is true so long as the adrenalectomized dog, whether with or without DCA maintenance, is still well nourished and tested only in the postabsorptive state. The authors conclude that adrenal cortical atrophy is an important factor in the production of the insulin hypersensitivity of the hypophysectomized dog. However, absence of an anterior pituitary factor (other than ACTH) is also of great importance in the production of this metabolic abnormality.

De Bodo, R. C.; Kurtz, M.; Sinkoff, M. W.; and Kiang, S. P. (*Dept. of Pharmacol., New York Univ. Coll. of Med., New York City*): EFFECTS OF ACTH, CORTISONE AND ADRENAL CORTICAL EXTRACT ON CARBO-

HYDRATE METABOLISM OF HYPOPHYSECTOMIZED DOGS. Proc. Soc. Exper. Biol. & Med. 80:345, June 1952.

Prolonged administration of ACTH and cortisone diminished and eventually abolished the insulin hypersensitivity of the hypophysectomized dog. Concomitant with these effects, ACTH and cortisone also abolished the secondary hypoglycemia of the intravenous glucose tolerance test and produced a marked blood sugar rise in response to epinephrine. In some animals, however, there appeared some degree of insulin resistance together with a diabetic type of glucose tolerance and an increased response above normal to epinephrine. The authors conclude that the adrenal cortical atrophy of the hypophysectomized dog exerts a significant part in the production of the insulin hypersensitivity.

Delore, Pierre (*Lyons*): INSULIN OVERDOSAGE. La presse Médicale 61:57-58, January 17, 1953.

The author advises the use of divided doses of insulin, particularly in diabetic coma, and emphasizes the danger from massive doses and sudden and significant blood sugar fluctuations. Dosage of insulin should be applied, as far as possible, in an individual manner and should aim at an optimal minimum physiologic dose.

Doerschuk, Albert P. (*Dept. of Chem., Columbia Univ., New York City*): MECHANISM STUDIES OF GLYCOGEN AND GLYCERIDE GLYCEROL BIOSYNTHESIS. J. Biol. Chem. 196:423-26, May 1952.

When glycerol-1-C^{14} was administered intraperitoneally to normal intact male albino rats, the distribution of the radioactive carbon (C^{14}) in the liver glycogen and carcass glyceride glycerol was established through measurements of the radioactivities of suitable degradation products. The distribution of liver glycogen C^{14} was considered to be consistent with initial oxidation and phosphorylation to dihydroxyacetone phosphate or D-3-phosphoglyceraldehyde or both, followed by the known reactions of glycolysis, the randomization of C^{14} occurring primarily through known processes involving carbon dioxide by beta-carboxylation of pyruvate. The relatively high quantity of C^{14} found in the secondary alcohol carbon of the glyceride glycerol was taken to indicate that randomizing processes played an important part in its formation. This suggests to the authors that one of the routes for its biosynthesis includes a reduction to glycerol or to a substituted glycerol of an intermediate in a higher state of oxidation, since all the randomizing processes accepted at present involve as intermediates materials in a higher state of oxidation than glycerol or its substitution products.

Drury, Douglas R.; and Wick, Arne N. (*Dept. of Physiol., Univ. of Southern California, Los Angeles, and Scripps Metabolic Clin., La Jolla, Cal.*): THE EFFECT OF B-HYDROXYBUTYRIC ACID ON GLUCOSE OXIDATION IN INSULINIZED ANIMALS. J. Biol. Chem. 196: 129-33, May 1952.

The effect of B-hydroxybutyric acid on glucose oxidation in insulin-treated, eviscerated rabbits was studied with the use of C^{14} labeled glucose. Although the disappearance rate of glucose was found to be little changed by the addition of B-hydroxybutyric acid, the rate of glucose oxidation was markedly reduced. The authors interpret these results as indicating that B-hydroxybutyric acid effectively competes with glucose in the terminal oxidation to carbon dioxide. They believe that in the extrahepatic tissues the primary action of insulin on glucose metabolism is concerned with the transfer of glucose into the cell. Its action on the terminal combustion of glucose is considered a secondary one, since the rate of oxidation of glucose could be readily reduced by increashing the oxidation of a competitive fuel.

Dury, Abraham; and Moss, Leo D. (*Dorn Lab. for Med. Res., Bradford Hosp., Bradford, Pa.*): EFFECT OF EPINEPHRINE AND INSULIN ON TISSUE ELECTROLYTES IN NORMAL AND DEMEDULLATED RATS. Proc. Soc. Exper. Biol. & Med. 80:199-203, June 1952.

The effect of epinephrine and insulin administration on the water and ionic content of plasma, skeletal muscle, and liver were compared in normal sham-operated and in adrenal-demedullated groups of rats (21 days after surgery). Histologic evidence was presented that the regenerated adrenal cortices appeared normal and medullary tissue was absent. A significant reduction in plasma and muscle potassium concentration was determined 60 minutes after epinphrine administration in the control and demedullated groups. A decreased plasma potassium level 60 minutes after insulin was determined in both groups. The authors believe that the apparent effect of insulin upon the

plasma potassium level in the intact animal was the resultant of "reflexly" elicited epinephrine secretion following insulin-induced hypoglycemia and not the effect of insulin per se.

Engelberg, Hyman (*Los Angeles*): HEPARIN THERAPY OF SEVERE CORONARY ATHEROSCLEROSIS, WITH OBSERVATIONS OF ITS EFFECT ON ANGINA PECTORIS, THE TWO-STEP ELECTROCARDIOGRAM AND THE BALLISTOCARDIOGRAM. Am. J. M. Sc. *224*:487-95, November 1952.

The author reports upon the effects in severe coronary atherosclerosis of the administration of 100 mg. of heparin twice weekly for a period of 6 to 12 months to 29 patients who had not responded to previous therapy. Eighteen had previously suffered an acute myocardial infarction.

Heparin reduced the incidence of anginal attacks in 55 per cent; in a few cases the improvement was very marked. The effect of heparin is probably not due to its anticoagulant or to its vasodilator action but possibly to its capacity to reduce the larger atherogenic lipoproteins to smaller aggregates and thereby to remove a lipoprotein sludge coating the intima. Both the exercise electrocardiogram and the ballistocardiogram afforded objective evidence of the beneficial effect of heparin. No dangerous reactions were observd.

The use of heparin offers a new approach to the prevention and therapy of atherosclerosis.

Escovitz, William E. (*Pulmonary Dis. Serv., Vet. Admin. Hosp., Long Beach, Cal.*): DISTURBANCE IN CARBOHYDRATE METABOLISM ASSOCIATED WITH AMITHIOZONE THERAPY. Am. Rev. Tuberc. *66*:373-77, September 1952.

Two cases of pulmonary tuberculosis are reported in which the patients developed disturbance in carbohydrate metabolism under prolonged amithiozone therapy. One developed diabetes, and the other had an aggravation of his previously well-controlled diabetic state.

Evseeff, George S. (*450 Cooper St., Royal Oak, Mich.*): INDICATIONS FOR THE INTRAVENOUS INJECTION OF INSULIN IN HYPOGLYCEMIA SHOCK THERAPY. J. Nerv. & Ment. Dis. *116*:310-20, October 1952.

The author reviews the treatment of schizophrenia with deep-coma insulin shock (Sakel's method) and presents a few of the controversial points regarding intravenous rather than intramuscular administration of insulin. Most of the evidence in the past supports the view that coma results more rapidly from intravenous insulin administration but that there is very little, if any, variation in the total dose required. In various series the dose required varied from 100 to 600 units in deep-coma therapy and from 12 to 90 units in the modified precoma hypoglycemia therapy (method of Polatin *et al.*). The author presents 12 patients treated by gradually increasing daily intravenous administration of insulin to shock levels. He concluded that (1) coma was produced more rapidly in the group given insulin by the intravenous route of administration than in a control group treated by the intramuscular route; (2) the overall treatment period was shortened; (3) a desired state of hypoglycemia was reached in 45 to 60 minutes; (4) the hypoglycemia could be terminated by oral glucose administration in most cases, rather than by intravenous glucose or sugar by stomach tube; (5) the incidence of serious complications of insulin shock therapy was notably absent.

Feldman, Maurice; and Weinberg, Tobias. (*Baltimore*): ABERRANT PANCREAS: A CAUSE OF DUODENAL SYNDROME. J. A. M. A. *148*:893, March 15, 1952.

In a series of 410 autopsies, aberrant pancreas of the duodenum was in 13.7 per cent. Aberrant pancreatic tissue may be found in all parts of the gastro-intestinal tract but is most often found in the stomach and duodenum. In this series, over 80 per cent of aberrant pancreactic nodules were found in the duodenum.

Symptoms are uncommon, but may arise as a result of enlargement, irritative secretion, ulceration, pressure, and complications, such as hyperinsulinism.

Flock, Eunice V.; Block, Melvin A.; Bollman, Jesse L.; and Mann, Frank C. (*Div. of Exper. Med., Mayo Found., Univ. of Minnesota, Rochester*): ALKALINE PHOSPHATE AND AMYLASE OF PLASMA AFTER HEPATECTOMY. Am. J. Physial. *170*:467-71, August 1952.

Although an increase in alkaline phosphates in plasma may occur after total hepatectomy in the dog, it is not an inevitable consequence of this operation. Tissues other than the liver definitely participate in the reg-

ulation of this enzyme in the blood. The increase in alkaline phosphatase of plasma occurring within 24 hours after partial hepatectomy in the dog is similar to that which may occur after total hepatectomy. This initial increase caused by partial hepatectomy is often followed in 1 or 2 days by a much larger increase, which might be of hepatic origin. The level of plasma amylase in the dog is not altered significantly by partial or total hepatectomy.

Foa, P. P.; Santamaria, L.; Berger, S.; Smith, J. A.; and Weinstein, H. R. (*Dept. of Physiol. and Pharmacol., Chicago Med. Sch., Chicago*): EFFECTS OF THE HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR (HGF), EPINEPHRINE AND INSULIN IN NORMAL AND DEPANCREATIZED DOGS. Proc. Soc. Exper. Biol. & Med. *80*:635-39, August-September 1952.

The hyperglycemia produced by hyperglycemic-glycogenolytic factor (HGF) and by epinephrine in the depancreatized dog with ketosis is greater in animals with mild ketosis than in animals wth severe ketosis. Since ketosis is believed to increase as liver glycogen decreases, these results suggest that the hyperglycemic response to HGF and epinephrine depends upon the amount of liver glycogen present. In the well-controlled depancreatized dog without ketosis, on the other hand, the hyperglycemic effect of HGF is greater than in the normal animal, suggesting that in the presence of the pancreas, the action of HGF is limited by the secretion of insulin. Similarly, in the well-controlled depancreatized dog without ketosis, the hypoglycemic effect of insulin is greater than in the normal animal, suggesting that in the presence of the pancreas the action of insulin is limited by the secretion of HGF. The authors suggest that HGF and insulin might be two mutually regulated pancreatic hormones and that their balanced secretion might be an important factor in the maintenance of a normal blood sugar concentration.

Foreign Letters. (*Denmark*): CAUSES OF DEATH IN DIABETICS. J. A. M. A. *149*:1592, August 23, 1952.

Heintzelman finds that since 1936 the annual number of deaths among diabetics in Denmark has remained fairly constant at about 20 per 100,000 of the population; the sex distribution during the three years under review has shown 38.5 men to 61.5 women. Per Hanssen also found in Bergen, Norway, no change in the total diabetes mortality between 1929 and 1940.

Most of Heintzelman's 2,620 deaths were due to degenerative changes in the heart. Renal disease and tuberculosis were also frequent causes of death; in childhood death was almost always due to diabetic coma. Cancer was remarkably rare as a cause of death among diabetics.

The rarity of cancer in general, and cancer of the stomach in particular, in diabetics may be more apparent than real and that the malnutrition induced by cancer renders the milder forms of diabetes so free from manifestations of this disease that it is often overlooked by a physician when writing a death certificate.

Forker, L. L.; and Chaikoff, I. L. (*Div. of Physiol., Univ. of California, Sch. of Med., Berkeley*): TURNOVER OF SERUM PROTEINS IN DIABETES AS STUDIED WITH S^{35} LABELED PROTEINS. J. Biol. Chem. *196*:829-40, June 1952.

Bisynthetically prepared serum proteins labeled with radioactive sulphur (S^{35}) were injected intravenously into depancreatized dogs in which diabetes was either not controlled or was brought under control by insulin treatment, and the disappearance of the labeled proteins from the circulation was followed for 1 or 2 weeks. From the data presented, the authors conclude that the degradation of serum proteins is not significantly changed in diabetes.

Frost, Douglas V.; Miller, Jonathan P.; and Richards, R. K. (*Abbott Labs., North Chicago, Ill.*): SOME CONSIDERATIONS REGARDING INVERT SUGAR AND DEXTROSE. J. Appl. Physiol. *4*:793-96, April 1952.

The authors found that invert sugar was better tolerated than dextrose, with less loss of reducing substances in the urine, when the two substances were compared on rapid injection (1.6 gm./kg./hour, equal to 100 gm. in 57 minutes to a 70-kg. person) in normal, ambulatory young men. Average retention was 94.5 per cent for invert sugar and 89.5 per cent for dextrose. This difference probably does not apply at ordinary rates of injection. These investigators conclude that further evidence is needed to establish the advantages of invert sugar as a total caloric source when given rapidly in large and repeated infusions.

Geiger, E. (*Univ. of Southern California, Los Angeles*): NUTRITIONAL PROBLEMS CONNECTED WITH DIABETES MELLITUS. J. Am. Dietet. A. 28:905-11, October 1952.

The nutritional problem associated with the prevention and dietary management of diabetes is presented. The effects of the various components in the diabetic diet upon the diabetes is discussed as is the value of fructose compared with that of glucose.

Gruber, C. M., Jr; Lee, K. S.; and Lashichenko, Z. (*Dept. of Pharmacol., Jefferson Med. Coll., Philadelphia*): EFFECT OF GLUCOSE ON OXYGEN CONSUMPTION AND RESPIRATORY QUOTIENT OF NORMAL AND DENERVATED MUSCLE. Proc. Soc. Exper. Biol. & Med. 80: 549-51, July 1952.

The oxygen consumption of innervated muscle in vitro is significantly greater in the presence of glucose than in its absence. The presence or absence of glucose produces no significant difference in the oxygen consumption of denervated muscle in vitro. No statistically significant difference was found in the respiratory quotients of innervated and denervated muscle with and without glucose in the medium.

Guthrie, Thomas C. (*New York City*): USE OF DIMERCAPROL IN TREATMENT OF PERIPHERAL NEURITIS. A.M.A. Arch. Neurol. & Psychiat. 68:199-204, August 1952.

The use of dimercaprol (BAL) in alcoholic and diabetic polyneuritis was first reported by Furmanski in 1948. He used smaller doses over longer periods than those recommended in treatment for heavy metal intoxication, i.e., 1.5 mg./kg. of body weight rather than 3-5 mg./kg. of body weight for 9 to 22 days (in 4 patients). A series of 22 cases of diabetic neuropathies is also reviewed in which 12 of 22 patients claimed some benefit subjectively, but no objective improvement. The present article reports the use of BAL in 18 cases of various forms of polyneuritis. There was no evidence that dimercaprol, whether in small or large doses, favorably influenced the course of the peripheral neuritis or neuronitis. As in previous series, there was frequent worsening of all symptoms immediately after the injection of BAL in many patients. In addition, objective increase in neurological signs took place.

Hall, G. F. M. (*King's Coll. Hosp. Med. Sch., London*): FACTORS IN THE ETIOLOGY OF DIABETIC GLOMERULOSCLEROSIS. Quart. J. Med. 21:385-404, October 1952.

Findings relevant to the etiology of diabetic glomerulosclerosis in a series of postmortem examinations of 120 diabetic patients are discussed in relation to findings in the literature. Diabetic glomerulusclerosis was mild in 31 cases and severe in 14 cases, the total incidence being 37.5 per cent. The incidence recorded in the literature varies between 16 and 82 per cent. In 100 nondiabetic controls, an isolated lesion of the glomeruluosclerotic type was found in only one case. Diabetic glomerulosclerosis is about 1.5 times as common in women as in men and is uncommon under the age of 40 years.

Hatch, Frederick T. (*New York City*): CRITIQUE OF CURRENT THEORIES ON THE PATHOGENESIS OF ARTERIOSCLEROSIS. Connecticut M. J. 16:887-94, December 1952.

In some cases of human and experimental arteriosclerosis, a disorder of lipid metabolism is manifested by abnormal patterns of lipids, or lipoproteins in the plasma. The pathogenesis of arteriosclerosis seems to be closely related to the accumulation of lipids in the lesions. Deposition of lipids is probably brought about either by an imbalance among the various species of plasma lipoproteins or by failure of the processes which ordinarily remove the filtered lipoprotein mixture. Arteriosclerosis has a focal distribution, local factors affecting some cells but not others. Although the condition is of almost universal occurrence in man, the consensus now is that arteriosclerosis is a disease and not solely an expression of the aging process.

Hayes, Mark A.; and Brandt, Ralph L. (*Dept. of Surgery, ,Univ. of Michigan Med. Sch., Ann Arbor, Mich.*): CARBOHYDRATE METABOLISM IN THE IMMEDIATE POSTOPERATIVE PERIOD. Surgery 32:819-27, November 1952.

During surgical convalescence, an insulin-resistant type of decreased carbohydrate tolerance occurs as a part of the metabolic response to trauma. Presumably, this decreased tolerance is not due to an interference with peripheral utilization.

Hurley, Lucille S.; and Morgan, Agnes Fay. (*Dept. of Home Economics, Univ. of California, Berkeley*): CARBOHYDRATE METABOLISM AND ADRENAL CORTICAL FUNCTION IN THE PANTOTHENIC ACID-DEFICIENT RAT. J. Biol. Chem. *195*:583-90, April 1952.

The authors studied the relationship of pantothenic acid deficiency in the rat to carbohydrate metabolism and adrenal cortical function. Pantothenic-acid-deficient rats subjected to lowered oxygen tension (349 mm. Hg) equivalent to an altitude of 20,000 feet for a period of 24 hours were unable to raise liver glycogen or blood sugar as were normal rats. Adrenal ascorbic-acid values were also lower in the deficient animals, whereas adrenal weights were increased. Administration of adrenal cortical extract to the deficient animals before the stress period enabled them to produce the normal carbohydrate response. This was not true of desoxycorticosterone acetate. Injection of pantothenic acid into the deficient rats before the stress period was effective in producing the normal response only when the animals had not reached the final stages of adrenal exhaustion.

These findings are interpreted as demonstrating that pantothenic acid deficiency imposes a stress on the adrenal cortex, resulting in exhaustion of the gland and adrenal hypofunction.

Ingebrigtsen, R.; and Langfeldt, E. (*Univ. of Oslo, Oslo, Norway*): PANCREATICOGASTRONOMY. Lancet 2:270-71, August 9, 1952.

In two patients the stump of the pancreas was implanted in the stomach after pancreaticoduodenectomy, an extensive resection of the gastric antrum being done at the same time to get rid of the gastric hydrochloric acid. Both patients made a good postoperative recovery. In both cases the pancreatic enzymes were found in the gastric contents after the operations. The operations therefore seemed to be technically and physiologically successful.

Jackson, S. H.; Savidge, R. S.; Stein, L.; and Varley, H. (*Manchester Royal Infirmary, Manchester, England*): CARCINOMA OF THE PANCREAS ASSOCIATED WITH FAT-NECROSIS. Lancet 2:962-67, November 15, 1952.

A case is reported of adenocarcinoma of the body of the pancreas with secondary deposits in the liver only, associated with widely disseminated fat necrosis in the subcutaneous tissues and bone marrow. This disseminated fat necrosis produced a striking clinical picture constituting a difficult diagnostic problem. The tumor and its secondaries were functionally active and were producing lipase in considerable quantities. The resulting high serum lipase level seems to have been the cause of the disseminated fat necrosis in the subcutaneous tissues and in the bone marrow. Venous thrombosis, vascular necrosis, and trauma were possible accessory factors in the production of the necrotic lesions. In cases presenting similar clinical features, estimation of the levels of pancreatic enzymes in the serum during life may assist the diagnosis.

Janes, R. G.; Bounds, G. W., Jr.; and Leinfelder, P. J. (*State Univ. of Iowa Coll. of Med., Iowa City*): OCULAR COMPLICATIONS IN THE RAT MADE DIABETIC WITH ALLOXAN. A. M. A. Arch. Ophth. *48*:415-19, October 1952.

In 21 rats made severely diabetic with alloxan, early cataractous changes were noted at one month, and complete opacity of the lens was observed at six months. When diets containing excess nicotinic acid were fed, there was some delay in cataract formation. This may have resulted from the lower food intake of the nicotinic-acid-fed group or from some effect of the nicotinic acid itself. Retinal change, consisting of a single hemorrhage, was observed in only one instance. After cataractous changes occurred, detailed observations of the fundus were impossible. Massive intraocular hemorrhage occurred in five of the animals fed the basal diet and in two animals fed the nicotinic acid diet.

Janes, Ralph G.; and Boeke, Lois S. (*Dept. of Anat., State Univ. of Iowa Coll. of Med., Iowa City*): INFLUENCE OF NIACIN AND PRISCOLINE ON KETONURIA, LIVER GLYCOGEN AND LIVER LIPID. Proc. Soc. Exper. Biol. & Med. *80*:591-94, August-September 1952.

When large amounts of niacin or priscoline were given daily to rats fasted for five days, an excessive excretion of urinary acetone bodies was noted in most of the animals. Niacin-injected rats had higher levels of liver glycogen; priscoline-injected animals had lower levels. Total liver lipid was not altered by either drug. There appeared to be no correlation between the amount of liver fat or liver glycogen and the presence of excess ketone bodies in the urine.

John, Henry J. (*Cleveland, Ohio*): MANAGEMENT OF DIABETIC PATIENTS DURING AN ACUTE INFECTION. Am. J. Digest. Dis. *19*:316-22, October 1952.

Eleven cases of diabetes in which infection occurred are presented; in only 2 instances was the diabetic state not aggravated. The remaining cases exhibited considerable disturbance in the carbohydrate metabolism. It is important to check each diabetic patient carefully, with blood sugar determinations when infection is suspected. This precaution is necessary so that the patient may be protected with added insulin during this added stress.

Keiding, Nils R.; Root, Howard F.; and Marble, Alexander (*The George F. Baker Clinic, New England Deaconess Hosp.*): IMPORTANCE OF CONTROL OF DIABETES IN PREVENTION OF VASCULAR COMPLICATIONS. J.A.M.A. *150*:964-69, November 8, 1952.

This study demonstrates clearly that, although the duration of diabetes may be correlated directly with the incidence of degenerative vascular disease, this is by no means the sole influence that is operative. Analysis of the data from various points of view has shown that the degree of control of diabetes over the years is of even greater importance than the duration.

Even under excellent or good control, retinopathy or arterial calcification develops in certain patients who have had long-standing diabetes because of the fact that ideal control of diabetes is almost impossible to attain with means now available. Ideal control implies the presence over many years of a constantly normal blood sugar level and sugar-free urine, reflecting entirely normal underlying metabolic processes. What the authors have termed excellent, good, fair, and poor control in reality means only varying degrees of inadequate control. A patient classified as having had excellent control has not by any means had ideal control throughout the years he has had diabetes.

The results of the study indicate that, at all stages of duration of diabetes, the incidence of retinopathy, arterial calcification, and nephropathy was significantly less in patients who had maintained excellent or good control of diabetes. It is concluded that only by careful and continuous attempts at control may the late complications of diabetes be prevented or postponed.

Kerr, Ehme H.; Stears, J. C.; MacDougall, Inna; and Haist, R. E. (*Dept. of Physiol., Univ. of Toronto, Toronto, Canada*): INFLUENCE OF GONADS ON GROWTH OF ISLETS OF LANGERHANS. Am. J. Physiol. *170*:448-55, August 1952.

Observations made over a period of 22 to 156 days after gonadectomy in male and female rats showed no significant changes in islet weight as compared with control animals. Repeated injections of estradiol benzoate, diethylstilbestrol, and progesterone caused significant elevations in the weight of the islets of Langerhans and in the islet weight per 100 gm. of body weight. The islet to acinar ratio in the pancreas was significantly increased by the injections of diethylstilbestrol. Injections of testosterone occasioned no significant change in the islet weight. It was concluded that the gonads have no indispensable influence on islet growth but that under some conditions and with large doses, certain female sex hormones can stimulate the islets and moderately increase their growth in intact rats.

Longo, Orlando F.; Sosa Gallardo, Carlos A.; and Ferraris, Alfredo: CONTRIBUTION TO PATHOGENESIS OF ACUTE PANCREATITIS. Archives des maladies de l'appareil digestif et des maladies de la nutrition *40*:1302, 1951.

A study was made of the three principal theories of the pathogenesis of acute pancreatitis: (1) the canalicular theory of reflux of bile into the pancreas, (2) the neurovascular theory of spastic conditions of chemical or reflex origin, leading to glandular ischemia and secondarily to alterations of the pancreas, and (3) the allergic theory.

Clinical observations and results of extensive experimentation on dogs led the authors to the conclusion that acute pancreatitis can have diversified origin. Whatever the causative factor, however, the mechanism remains the same: Irritation of the sensory splanchnic fibers provokes intensive vasodilatation, followed by edema and hemorrhages. If the process continues, changes in the pancreatic cells take place, and ultimately autocatalysis and necrosis may develop.

Lyon, I.; Masri, M. S.; and Chaikoff, I. L. (*Div. of Physiol., Univ. of California Sch. of Med., Berkeley*): FASTING AND HEPATIC LIPOGENESIS FROM C^{14} ACETATE. J. Biol. Chem. *196*:25-32, May 1952.

The authors report that fasting diminished drastically the capacity of the surviving liver slices prepared from

normal rats to form fatty acids from added C^{14} acetate. This effect was observed as early as 12 hours after food was withheld, and by the time 18 hours had elapsed the liver almost completely lost its ability to incorporate acetate carbon into fatty acids.

The likelihood that the absence of carbohydrate in the diet is principally responsible for the loss in lipogenesis at these early intervals was shown in four types of experiments: (1) The administration of extra carbohydrate alone, just before the start of the fast, delayed the decline in the lipogenic activity of the liver; (2) even when liver lipogenesis was depressed following fasting, a single administration of 5 gm. of glucose resulted in the restoration of lipogenesis from added acetate to an extent exceeding that observed in rats fed ad libitum; (3) a single feeding of 2.5 cc. of corn oil, approximately equal in caloric value to 5 gm. of glucose, did not restore lipogenesis in the fasted liver; (4) although the feeding of an isocaloric amount of a casein hydrolysate did not stimulate lipogenesis from added acetate, the extent of stimulation was in no way comparable with that observed when glucose was fed. The mechanism of glucose action on hepatic lipogenesis is discussed.

Martin, M. Spencer (*King's Coll., Hosp.*): CHARCOT JOINTS IN DIABETES MELLITUS. Proc. Roy. Soc. Med. 45:503-06, August 1952.

Painless neuropathic ulcers and Charcot joints, although often stated to be common only in tabes dorsalis and syringomyelia, are by no means uncommon in diabetes. Autonomic nerve damage, ischemia, or sepsis cannot explain adequately the pathogenesis of a neuropathic arthropathy. Diabetic neuropathy shows a predilection for nonmyelinated nerve fibers which causes pain fibers to be involved early. It appears that the "mechanical theory," postulating that loss of afferent impulses allows minor trauma to damage the joints, has most to recommend it. The presence of histologic evidence of nerve degeneration in all the 4 cases with diabetic arthropathy in which nerve biopsies were obtained and the absence of Charcot joints in patients without diabetic neuropathy in the diabetic population attending King's College Hospital support the belief that these bone changes are truly neuropathic and develop only in the presence of nerve disease and continued weight bearing.

Both neuropathic skin and joint lesions are the result of the underlying nerve disorder consequent upon poor diabetic control, and it is therefore most important that attention be directed toward treatment. Unfortunately there is, as yet, no specific cure for this complication of diabetes mellitus beyond rigid control of the metabolic disorder. With adequate diabetic treatment, however, recovery may be expected in about 60 per cent of cases within six months to two years, unless the neuropathy has been of long standing. With recovery of the nerve disorder the progress of the bone changes appears to be halted.

Milch, Lawrence J.; Redmond, Robert F.; Calhoun, William W.; Chinn, Herman I.; and the Cardiovascular Research Group (*U.S.A.F. Sch. of Aviation Med., Randolph Air Force Base, Texas*): EFFECTS OF ADENOSINE-5-MONOPHOSPHATE ON SERUM AND AORTAL LIPIDS IN THE CHICKEN. Am. J. Physiol. 170:346-50, August 1952.

Adenosine-5-monophosphate was administered in low dosage to 6-week-old cholesterol-fed cockerels and in comparatively high dosage to 2-year-old atherosclerotic hens. In the cholesterol-fed cockerels, serum lipid analysis indicated that the administration was associated with a pronounced fall in total cholesterol and some trend toward lower values in serum beta-globulin concentration. No change was noted in the serum phospholipid/cholesterol ratio. In the atherosclerotic hens, higher dosages induced little change in the serum cholesterol concentration, but significant increases were noted in the phospholipid/cholesterol ratios. Similarly, there was some suggestion of an increase in the serum concentration of the S_f 12-20 class of liproteins. It was further observed that administration of adenosine monophosphate was associated with a significant decrease in the fat and cholesterol concentration of atherosclerotic hen aortas.

Moreau, René; Deuil, Roger; and Crosnier, Jean (*Paris*): TREATMENT OF DIABETIC COMA. SERIOUSNESS OF INTRACELLULAR DEHYDRATION. ITS CORRECTION. press méd. 60:1317-18, October 4, 1952.

In a series of 15 cases the authors have studied the disorders of hydration in diabetic coma. In addition to extracellular dehydration, there is frequently a plasmatic hypertonia with predominating intracellular dehydration. The severity of the disorders of consciousness seems

to be more related to intracellular dehydration than to all other biological disorders. Simple rules for controlled rehydration are given and are applicable even without the aid of a hospital laboratory.

Morrow, Thomas F.; Laucks, S. Philip; and McKnight, William K. (*Philadelphia, Pa.*): INSULIN COMA AND GROUP PSYCHOTHERAPY. A.M.A. Arch. Neurol. & Psychiat. *68*:491-97, October 1952.

The therapeutic advantage of insulin coma over electroshock in the treatment of schizophrenia is stressed; namely, that mental reintegration of the patient takes place through an organized rational and connected program of psychotherapy rather than through reintegration after temporary confusion clears. The authors point out that other coma-producing drugs do not have the same beneficial effect as insulin. The physiologic mechanism is not explained, although the psychologic functions are adequately postulated. (Complications of such therapy are not mentioned.) The total time of treatment for patients undergoing almost daily coma therapy averaged 54 days.

Nardi, George L. (*Harvard Med. Sch., Massachusetts Gen. Hosp., Boston*): METABOLIC STUDIES FOLLOWING TOTAL PANCREATECTOMY FOR RETROPERITONEAL LEIOMYOSARCOMA. New England J. Med. *247*:548-50, October 9, 1952.

Total pancreatectomy was carried out as a part of a radical excision of a retroperitoneal leiomyosarcoma. The patient survived for one year. The "brittle" type of diabetes developed and required only 20 units of insulin daily. There was no fatty infiltration of the liver. Radioactive phospholipid studies suggest that absence of the pancreas in man does not result in abnormalities of phospholipid metabolism as reported in dogs. The patient's nutritional status was better without pancreatin than with it. Serum amylase and lipase were repeatedly present in normal concentrations after total pancreatectomy.

Norberg, Bo (*Biochemical Dept., Karolinska Inst., Stockholm*): ALKALINE LIVER PHOSPHATASE IN REGENERATING RAT LIVER. INFLUENCE OF ALLOXAN DIABETES, INSULIN, AND BAYER 205. Acta. endocrinologica *11*:156-70, October 1952.

The regeneration of mass and alkaline phosphatase of the liver after lobectomy has been studied in normal and alloxan-diabetic rats, as well as in insulin-treated diabetic rats and in rats given Bayer 205. The cyanide-sensitive phosphatase II is mainly responsible for the increase at 24 and 48 hours' regeneration. Alloxan diabetes, which upsets many metabolic processes, especially glucose oxidation, fails to inhibit the regeneration of liver mass and alkaline phosphatases. Insulin does not improve regeneration in diabetic rats, nor does Bayer 205 impair the regeneration. Possible reasons for these findings are discussed. It is suggested that priority is given in allocation of energy for protein synthesis. In a few experiments the production of phosphatase II was increased much beyond normal, but the mechanism of this activation of protein formation remains obscure.

Parmelee, A. H. (*Beverly Hills, Cal.*): THE NEWBORN INFANT: AN INTERPRETATIVE REVIEW. J. Pediat. *41*:591-612, November 1952.

The general endocrine imbalance of a diabetic woman further disturbed by the endocrine changes of pregnancy may profoundly influence the intra-uterine environment and alter the physiologic processes of her fetus in a variety of ways. Knowledge in this field is still incomplete. In the meantime, certain methods of intelligent care are suggested by the facts at hand—prenatally, adequate control of the diabetes and substitution therapy when indicated; natally, wise selection of type of delivery, administration of oxygen in surgical deliveries, and restriction of sedatives; postnatally, administration of oxygen and restriction of fluids in the first two to three days. Whether or not glucose should glycemia or to treat it if present is an unsettled question.

Pedowitz, Paul; and Shlevin, Edmund L. (*Depts. of Obstet. and Gynec. and Med., New York State Coll. of Med., and Jewish Hosp. of Brooklyn, N. Y.*): THE PREGNANT DIABETIC. Bull. New York Acad. Med. (Second Series) 28:440-453, July 1952.

Uncontrolled diabetes and pregnancy are basically incompatible, and despite the advances in our knowledge, diabetes and pregnancy still present a formidable problem indicated by a viable fetal loss of 18.4 per cent in 1.011 diabetic pregnancies.

An increased incidence of toxemia is a factor in the high fetal mortality. The greatest number of intrauterine deaths occur from the 36th week of gestation on. Toxemia and keto-acidosis are the two prime factors responsible for this occurrence, and it would therefore seem advisable to terminate the pregnancy even earlier than the 36th week, in order to increase fetal salvage. In order to recognize subclinical acidosis, the patient should test the urine daily for acetone.

With vaginal delivery there is greater risk of intrapartum deaths and traumatic delivery, for these infants are large, do not tolerate labor well, and may die as a result of anoxia. Cesarean section during the 36th to 38th week is indicated in the patient with uneffaced cervix (in primiparae and some multiparae).

Recurrent episodes of hypoglycemia are most likely to occur in the first trimester of pregnancy, this may prove to be a factor responsible for the increased incidence of congenital anomalies.

The authors believe the use of hormonal therapy does not appear to be indicated; the fetal loss in a nonendocrine-treated series is only 1.5 per cent greater than that reported for a treated series.

Please, N. W. (*Dept. of Statistics, Univ. Coll., London*): STATISTICAL EXAMINATION OF MULTIPLE-DOSE ASSAYS. Biochem. J. 52:75-76, September 1952.

An explanation is given for statistical examination of multiple-dose assays of glycogenolytic factor in insulin, as applied by Audy and Kerly (Biochem. J., 52:70-74, September 1952).

Queries and Minor Notes (*Miami, Fla.*): TREATMENT OF OSTEOARTHRITIS. J.A.M.A. 150:1163, November 15, 1952.

Treatment of osteoarthritis by means of an extract derived from pregnant mammalian liver was described recently at the Second International Gerontological Congress, in St. Louis, during September, 1951. A series of 110 cases had been studied; 84 per cent showed evidence of improvement. Results were excellent in 22 per cent, good in 46 per cent, and fair in 16 per cent; 16 per cent failed to respond. The same extract was said to possess the property of quickly reversing the "symptom-syndrome of peripheral neuropathy both in diabetics and nondiabetics."

Apparently, no other report has thus far been published dealing with this form of treatment for arthritis. The work is not known to have been checked or confirmed by independent observers; until this has been done, an opinion as to the value of this procedure must be reserved.

Queries and Minor Notes (*Michigan*): BLOOD SUGAR LEVEL DURING PREGNANCY. J.A.M.A. 150:1443, December 6, 1952.

The blood sugar rises from 10 to 20 per cent during pregnancy. If sugar continues to be present in the urine, a glucose tolerance test may be indicated. Any patient who has an unusually large baby should be checked carefully for signs of early diabetes.

Queries and Minor Notes (*Union City, N. J.*): IMPOTENCE AND DIABETES. J.A.M.A. 150:1361, November 29, 1952.

If the condition occurs after diabetes of long duration, the influence of premature vascular disease and of neuropathy must be considered. Psychological factors are often of great importance, as they are in nondiabetics.

Careful and continuous control of the diabetic condition, an adequate diet, the avoidance of excessive physical and emotional fatigue, and psychotherapy are indicated.

Revell, Samuel T. R., Jr. (*Dept. of Med., Univ. of Maryland Sch. of Med., Baltimore*): GLOBIN INSULIN WITH ZINC IN DIABETIC OUTPATIENTS. Bull. School Med. Univ. Maryland 36:156-62, October 1951.

The author finds globin insulin to be an effective form of substitution therapy in the diabetic patient requiring a relatively small dose of insulin for satisfactory control. It exhibits a moderately wide range of safety in diabetic patients whose failure to follow instructions has led to repeated instances of diabetic coma. In divided doses, globin insulin has been found to be an extremely efficient tool in the successful management of "brittle" diabetics.

Ricketts, Henry T. (*Dept. of Med., Sch. of Med., Univ. of Chicago*): MODERN TREATMENT OF DIABETES MELLITUS. J.A.M.A. *150*:959-61, November 8, 1952.

The treatment of diabetes mellitus has four principal objectives: (a) the relief of symptoms, (b) the maintenance of normal nutrition, (c) the preservation of the insulin-producing capacity of the pancreas, and (d) the prevention or reduction of complications.

The objectives of the treatment of diabetes are best attained by the use of quantitative diets, NPH insulin in most cases in which insulin is needed, and control of the blood sugar level and glycosuria as strictly as is compatible with the avoidance of hypoglycemia.

Diabetes itself is capable of causing arterial degeneration. Most patients with mild or well-controlled diabetes have little or delayed vascular disease; although some do have severe vascular disease, others escape this complication. Control, then, is not a sure preventive, but it helps sufficiently to justify the physician's exerting his best efforts to maintain it in all cases.

Rippy, Edwin L. (*Dallas, Texas*): THE IMPROVED OUTLOOK FOR THE DIABETIC PATIENT. J.A.M.A. *150*:961-63, November 8, 1952.

One of the most dramatic human-interest stories of our times is the story of diabetes. It has the elements of early tragedy, scientific lethargy and confusion, magnificent effort, and a great triumph. It is a story to which many persons have contributed immortal chapters. It is an unfinished story to which a challenged mind will someday dictate a fitting conclusion. It is a story that will inspire medical imagination and effort for all time to come.

In early days the rule was literally "eat and die or starve and live . . . then die." Now, the story has changed; the diabetic eats a well-rounded diet which, thought regulated, actually differs little from the average diet; he remains healthy and well for many years. Diabetic children grow robust and thrive into adulthood. Emaciation and multiple-symptom pictures are seen infrequently. Life is restored to the patient dying in acidotic coma. The diabetic lives as a normal human being and can live almost as long as he is taught to or wants to live.

As a result of the great triumph of the discovery of insulin and its subsequent modifications, the lot of the diabetic today is good. It is obvious, however, that if the outlook of the diabetic of the future is going to continue to improve, further knowledge of this disease will have to be discovered by the scientist and the clinician.

Robbins, S. L.; Rogers, J.; and Wollenman, O. J. Jr. (*Mallory Inst. of Path. and the Boston City Hosp., Boston*): INTERCAPILLARY GLOMERULOSCLEROSIS: A CLINICAL AND PATHOLOGIC STUDY. III. A PATHOLOGIC STUDY OF 100 CASES. Am. J. Med. *12*:700-05, June 1952.

The authors conclude from their study that the Kimmelstiel-Wilson lesion, or nodular intercapillary glomerulosclerosis, is a specific histologic lesion found only in diabetes. Although nephrosclerotic and glomerulonephritic changes may closely simulate this lesion, specific histologic points of differences are described. Much of the current confusion in the literature is ascribed to the use of the term intercapillary glomerulosclerosis in a purely descriptive sense. It is contended that the general use of the term has failed to take cognizance of the fact that Kimmelstiel and Wilson in their original description segregated from this diffuse variety of intercapillary lesions a specific peripheral nodular variety that, according to them, remains to this date a distinct entity. It is recommended that the more specific term, Kimmelstiel-Wilson lesion (or nodular intercapillary glomerulosclerosis) be substituted for the previous terminology.

Robinson, P. L.; and Baker-Bates, E. T. (*Clatterbridge Gen. Hosp., Bebington, Cheshire, England*): A NEW DIABETIC CHART. Brit. M. J. *2*:919-21, October 25, 1952.

A new form of diabetic chart for use in hospital standardization is described and illustrated. The importance is stressed of recording on the chart the time over which specimens of urine are secreted. This record is achieved by providing chart space for the time the bladder was previously emptied as well as the time the urine specimen was passed. Attention is drawn to the fact that many diabetics satisfactorily standardized on insulin have glycosuria immediately after a meal; therefore, routine, short-period specimens before meals are the most helpful. A simple method is described for determining the relation of the renal threshold to a single blood sugar result.

Rogers, Joseph; Robbins, Stanley L.; and Jeghers, Harold. (*Boston City Hosp.; Dept. of Med., Tufts Coll. Med. Sch.; and the Mallory Inst. of Path., Boston*): INTERCAPILLARY GLOMERULOSCLEROSIS: A CLINICAL AND PATHOLOGIC STUDY. II. A CLINICAL STUDY OF 100 ANATOMICALLY PROVEN CASES. Am. J. Med. *12*:692-99, June 1952.

In the hope that certain clinical differences might be revealed that would be of help in establishing the diagnosis of intercapillary glomerulosclerosis in any individual patient, the authors compared 100 diabetics who had proved intercapillary glomerulosclerosis with 176 diabetics not having this lesion. They noted the following points of interest: With increasing duration of the diabetes there was a definite increase in the incidence of intercapillary glomerulosclerosis. Although only 14 per cent of the patients with diabetes of less than four years' duration had this renal lesion, the incidence rose to 64 per cent in patients with diabetes of 10 to 14 years' duration. No significant difference was found in the severity of the diabetes in the two groups. Patients with this specific glomerular lesion tended to show less glycosuria than was expected from the associated levels of hyperglycemia. Hypertension, albuminuria, azotemia, and cardiac failure all were more frequent and more severe in the patients with intercapillary glomerulosclerosis. Uremia, cardiac decompensation, and cerebrovascular accidents were also significantly more prevalent. Cases in which there was most advanced involvement of the kidneys, showed greatest edema, hypertension, albuminuria, and cardiac failure. Moreover, the diabetes was of longer duration. Difficulties in clinical diagnosis are illustrated by the finding that the classic pattern occurred in only 25 of the 100 cases of intercapillary glomerulosclerosis. It also occurred in five cases of the control group of diabetics.

Rogers, Joseph; and Robbins, Stanley L. (*Boston City Hosp.; Dept. of Med., Tufts Coll. Med. Sch., and the Mallory Inst. of Path., Boston*): INTERCAPILLARY GLOMERULOSCLEROSIS: A CLINICAL AND PATHOLOGIC STUDY. I. SPECIFICITY OF THE CLINICAL SYNDROME. Am. J. Med. *12*:688-91, June 1952.

The clinical records of 229 diabetics were evaluated on strictly clinical grounds as to the "possible" or "probable" presence of intercapillary glomerulosclerosis. The clinical diagnosis was then correlated with the autopsy record. Of the 41 cases selected clinically as having intercapillary glomerulosclerosis, only 28 proved to have the anatomic lesion, a false positive error of 32 per cent. Thirty-eight anatomic instances of the lesion were not selected because no apparent diagnostic clinical features were present; hence, of a possible 66 cases, only 28 (43 per cent) were correctly identified. The authors were unable to find a clear-cut clinical syndrome, even in the presence of diabetes mellitus. They contend that a diabetic not having this anatomic lesion may present the so-called classic features of intercapillary glomerulosclerosis.

Root, Howard F.; and West, Kelly M. (*Boston and Oklahoma City*): THE INCREASING INCIDENCE OF CORONARY ARTERIOSCLEROSIS IN DIABETES MELLITUS: PRELIMINARY MANUSCRIPT. J. Oklahoma M. A. *46*:6-11, January 1953.

Coronary arteriosclerosis has been the chief cause of death in diabetics for several years, and its incidence is increasing. Coronary arteriosclerosis was the major cause of death in 51 per cent of a recent autopsy series (100 cases with onset of diabetes after age 21). The very high incidence of myocardial infarction in diabetics is due mainly to an acceleration of the rate of coronary sclerosis, but the increased frequency of obesity and hypertension (usually related to nephropathy) also favors myocardial infarction. The incidence of cerebrovascular disease in the diabetic does not differ greatly from its incidence in the nondiabetic. Since renal infection accounted for 8.5 per cent of the deaths in this series, great emphasis should be placed on the discovery, prevention, and aggressive treatment of all urinary tract infections. There is considerable recent evidence to show that careful control of diabetes will delay the onset of degenerative vascular lesions in younger diabetics. Investigation is needed to determine whether or not careful control of diabetes will postpone the development of coronary arteriosclerosis.

Schieve, James F.; and Wilson, William P. (*Dept. of Med. and Psychiat., Duke Univ., Durham, N. C.*): FAILURE OF DESOXYCORTICOSTERONE GLUCOSIDE TO ALTER CEREBRAL VENOUS SUGAR CONCENTRATION IN MAN. J. Clin. Investigation *31*:984-85, November 1952.

Intravenous administration of desoxycorticosterone glucoside (DCG) in man has been previously reported to cause an immediate liberation of sugar from the brain

into cerebral venous blood. Desoxycorticosterone glucoside, in the dosage used, did not narrow arterialcerebral venous glucose difference. In no instance did cerebral venous blood sugar content surpass or approach arterial levels.

Schwartz, Edward D.; and Goodman, Joseph I. (*Mt. Sinai Hosp., Cleveland*): GROUP THERAPY OF OBESITY IN ELDERLY DIABETICS. Geriatrics 7:280-83, September-October 1952.

The successful treatment of obesity, in nondiabetics as well as in diabetics, is frequently difficult because of potent psychologic forces acting antagonistically toward efforts at weight reduction. The group-therapy method admittedly has the disadvantage that it can be applied only to a relatively small group at a time; however, the method yields worth-while results in many cases that are resistant to the usual management of obesity employed in the clinic. Its effectiveness in elderly patients is particularly interesting and gratifying. These patients frequently feel that no one is interested in them any more and that their condition is quite hopeless. Their enthusiastic response to close personal attention encourages similar therapy in other disease conditions.

Searle, G. L.; and Chaikoff, I. L. (*Div. of Physiol., Univ. of California Sch. of Med., Berkeley*): INHIBITORY ACTION OF HYPERGLYCEMIA ON DELIVERY OF GLUCOSE TO THE BLOOD STREAM BY LIVER OF THE NORMAL DOG. Am. J. Physiol. *170*:456-60, August 1952.

The body glucose pool of normal dogs in the postabsorbtive state was labeled with C^{14}-glucose, and the rate at which glucose is furnished to the blood stream by the liver was determined from the rate of decline in the specific activity of plasma glucose with time. The liver of a 5.6-kg. dog delivered about 1.1 gm. hour to the animal's circulation; that of an 8.6-kg. dog delivered about 1.5 gm. hour. The transfer of glucose from liver to blood stream stopped upon the sudden introduction of a massive dose of glucose into the blood stream.

Seibert, Richard A.; Huggins, Russell A.; and Saxton, Ruth. (*Dept. of Pharmacol., Baylor Univ. Coll. of Med., Houston, Texas*): EFFECTS OF INTRAVENOUS INFUSION OF POTASSIUM ON LIVER GLYCOGEN. Am. J. Physiol. *170*:461-66, August 1952.

The author reports studies on liver glycogen and liver potassium and plasma sugar and plasma potassium in female dogs after infusion of isotonic potassium chloride. Hyperglycemia occurs regularly from sodium barbital and morphine sulfate, but the mechanism of its production by the two anesthetics appears to be different. The infusion of potassium chloride results in a marked decrease in liver glycogen, whether the anesthetic used is sodium barbital or morphine-pentobarbital. This release of glycogen is not accompanied by an increase in blood glucose. When glycogen moves out of the liver cells, the size of the cells decreases, the chloride space increases, and protein and fat contents remain constant. When the calculation is made on a wet weight basis, there is no evidence of an increased concentration of potassium in the liver. However, on a dry weight basis, liver potassium increses approximately 18 per cent. These data more closely approximate the concept of Fenn—that as glycogen is deposited in the liver, it is accompanied by water, potassium, and acid-soluble phosphate—rather than the viewpoint of Kaplan and Chaikoff—that glycogen is deposited dry.

Shacter, Bernard; and Entenman, Cecil. (*Div. of Biol. and Med. Sci., U. S. Naval Radiological Defense Lab., and Lab. of Exper. Oncology, San Francisco*): EFFECT OF CORTISONE, CORTICOTROPIN AND ADRENALECTOMY ON PLASMA SULFHYDRYL AND PROTEIN LEVELS. Am. J. Physiol. *170*:442-47, August 1952.

The authors report studies on the level of sulfhydryl and protein in the plasma of rats receiving cortisone or corticotropin and after adrenalectomy. Both cortisone and corticotropin partially prevented the fall in plasma sulfhydryl which normally occurs after laparotomy. Whereas corticotropin administration did not affect the plasma protein content of laparotomized animals, cortisone produced significantly a higher concentration than was observed in saline-treated controls. Adrenalectomized and sham-operated animals exhibited similar decreases in the plasma sulfhydryl content, but only female rats showed a significant fall in the plasma protein concentration after operations. It is suggested that cortisone and corticotropin may retard wound healing by inhibiting the utilization of sulfhydryl groups essential for tissue regeneration.

EDITORIALS

STEROID DIABETES

The term "steroid diabetes" has come into such wide use in recent years that it merits editorial comment and definition. Properly the term is applied in clinical medicine to a diabetic state resulting from an excess of adrenal steroids which have a high degree of carbohydrate activity. Such steroids interfere with the action of insulin, impair carbohydrate utilization and augment the formation of sugar from protein. The most potent are cortisone and hydrocortisone, the latter being slightly more active than the former, according to assays on animals.

Steroid diabetes was first produced experimentally in the normal rat by Ingle who in 1941 administered large doses of cortisone.[1] The condition has certain features, first described by Ingle and associates in the rat, which distinguish it from pancreatic diabetes.[2] In steroid diabetes there is a relative insensitivity to insulin. Since the condition is attributable in part to excessive gluconeogenesis from protein under the catabolic influence of adrenal steroids, it is associated with a negative nitrogen balance which is not corrected by administration of insulin. In addition, steroid diabetes, in contrast to pancreatic diabetes, is temporary, subsiding when the source of excess adrenal steroids is removed.

The occurrence of steroid diabetes in man is limited principally to patients with spontaneous adrenal cortical hyperfunction of the type which produces Cushing's syndrome[3] and to some patients who are receiving cortisone, hydrocortisone or corticotropin in large doses for therapeutic purposes. It is thus apparent that steroid diabetes is relatively rare, and that large amounts of carbohydrate-active steroids are necessary for its production. In cases of "ordinary" diabetes there is no convincing evidence of hyperfunction of the adrenal cortex, except transiently during severe diabetic acidosis.[4] Insufficiency of the islet tissue increases the likelihood that diabetes will result from the presence of excessive amounts of adrenal steroids.[5]

While the term "steroid diabetes" should be limited to those diabetic states which result from an excess of adrenal steroids, it should be recognized that the presence of some adrenal steroids is necessary for the maintenance of the ordinary diabetic state. Many of the features of diabetes disappear if the adrenals of the diabetic are destroyed or removed,[6] and the diabetic state is restored if cortisone or hydrocortisone is administered. It appears that the adrenal hormones play what Ingle has called a "permissive" role in ordinary diabetes; they do not cause the diabetes but their presence is necessary for its maintenance.

The paper in this issue of DIABETES by Bookman[7] and associates describes steroid diabetes in the human being resulting from administration of large doses of corticotropin or cortisone. Conn and associates[8] previously have described the production of steroid diabetes by corticotropin, and some of its characteristics. The capacity of corticotropin, as well as of cortisone and hydrocortisone, to induce diabetes in man, shows that the secretory capacity of the adrenal glands, in some individuals at least, is great enough during stimulation to reproduce the diabetogenic effects of large doses of the carbohydrate-active adrenal steroids.

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INSULIN RESISTANCE

Insulin resistance may or may not be associated with the visible manifestations of allergy to insulin. Although the majority of patients with minor, transitory, allergic reactions to insulin are not noticeably resistant to insulin, one rightly looks for allergy to insulin as a possible cause of sever insulin resistance. In the last decade, the study of insulin resistance has been advanced by the application of several new methods. Lerman[1] and Lowell,[2,3] selecting patients because they were insulin resistant (with or without associated local allergy) have presented strong evidence for an immunologic mechanism. The same immunologic methods have indicated that antibodies to administered insulin may be produced in rabbits.[4] Insulin recrystallized six times is much less antigenic than commercial insulin[5] and the use of insulin prepared from human pancreas may be normally effective in the presence of resistance to the usual commercial insulin.[3] Such results indicate that the allergy to administered insulin is due either to some contamination of the protein hormone, or to differences in the actual structure of insulin from different sources, to which these few patients are susceptible.

Further evidence of the part which allergy may play in insulin resistance has appeared since the control of allergic reactions by corticotropin (ACTH) has been possible. Howard[6] treated a patient, who had marked resistance and allergy to insulin, with corticotropin and was able to restore the patient to a stage of mild diabetes for which no insulin was needed. Sera of this and of other insulin resistant patients were examined for their effect on the action of insulin on the isolated rat diaphram.[7] There was striking inhibition of the effect of insulin in vitro by the sera of patients requiring 300 units of insulin per day or more. In the patient who had been treated with corticotropin, this inhibitory action of the serum was no longer present. Finally, Marsh and Haugaard[7] have shown that the serum of insulin resistant patients behaves differently from the hormones which inhibit the action of insulin in vitro. Thus in the presence of antibodies, less insulin is bound to the rat diaphragm: antagonistic hormones appear not to prevent this binding of insulin to tissue but to inhibit its subsequent metabolic action. These results emphasize the importance of immune reactions in insulin resistance. The preliminary differentiation of immunological and hormonal types of insulin resistance by new methods suggests that this obscure corner of diabetes may be considerably enlightened in the future.

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A PRE-DIABETIC STATE IN PARENTS OF OVERWEIGHT BABIES

It is widely recognized that maternal diabetes bears a close relationship to production of abnormally large babies as well as to hydramnios, a high fetal mortality and perhaps toxemia. It has been clearly shown by Miller, Kriss and Futcher and others, that abnormally large children may be born to mothers who have no evidence of diabetes at the time of birth (as judged by existing methods) and who later develop diabetes.

W. P. U. Jackson,[1] in his recent article in the British Medical Journal, offered fresh, carefully studied and convincing evidence along these lines. He found that 62 per cent of women who developed overt diabetes after childbearing claimed to have had before becoming diabetic at least one baby over 10 pounds in weight at birth; 31 per cent of the babies of these women were over 10 pounds as compared with 4.6 per cent of the babies of women in the control group. One of the most engaging parts of Jackson's studies and one which appears to be a new contribution to the knowledge of internal maternal environment must be the dominant

factor; here according to current concepts the pituitary growth hormone may play an important part. In the case of the "pre-diabetic fathers," the factor of inheritance must be the determining factor.

Jackson contends that when a woman gives a history of having had several large babies, the diagnosis of a pre-diabetic state is justified to such an extent that treatment should be started before glycosuria or hyperglycemia are known to exist. He believes that a pre-diabetic state must be present from the first pregnancy resulting in the delivery of a baby over ten pounds in weight to the time at which active diabetes is demonstrable. Critical students of the problem will find it difficult to accept these ideas as completely valid.

The whole concept of the pre-diabetic state is an intriguing one and may well prove of importance in advancing the knowledge regarding the etiology of human diabetes. One might ask what must be the evidences of diabetes before the diagnosis can be made. We need not wait for cardinal symptoms before we are justified in considering diabetes to be present. Is the condition certain to be present if the blood sugar two or three hours after eating is abnormally high even to a slight degree? If this is true, then diabetes exists if the blood glucose is consistently elevated in the absence of unusual endocrine or hepatic disease. Taken in this light, diabetes then varies only in the degree of mildness or severity and pre-diabetes does not exist unless it can be predicted when no measurable evidence of it is present by available chemical means.

The practical importance of the problem is concerned with the advantage to the patient of knowing of the existence of mild diabetes or the pre-diabetic state. This is a matter which concerns all interested in diabetes detection. One can agree with Jackson that it is of value in that it at least gives the physician the opportunity of prescribing a diet limiting the carbohydrate, and, if necessary, the caloric intake. The benefit which may come from this policy over a long period of years will have to be evaluated by comparison of the experience of those who do not change in dietary habits.

A point of immediate and practical value, which is emphasized by the author, is that the birth of abnormally large children calls for a careful evaluation of carbohydrate tolerance in the mother. She should have attention to the matter at the time and at regular intervals for the rest of her life.

E. PERRY MCCULLAGH, M.D.

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GROWTH OF THE ISLETS OF LANGERHANS

Ever since diabetes was produced by pancreatectomy, efforts have been made to learn more of the behavior of the islets of Langerhans. At present the principal methods for studying the islets are: 1) Counting the islands in serial or frequent microscopic section; 2) the qualitative appraisal of their size and condition on microscopic examination; 3) estimation of the islet volume (or weight); 4) determination of the insulin content of the pancreas; 5) estimation of insulin secretion by grafting the pancreatic vein of a test animal to the circulation of a depancreatized animal. One of the most useful of these procedures has been the measurement of islet volume under various experimental conditions. The article by Kinash and others, published in this issue of DIABETES, is a valuable addition to their previous work. It will remind physicians of a number of facts which they cannot see in their patients but which they might like to know.

The capacity of the islet to grow differs greatly in different species and is less in adult than in young animals. In rats, which have a great capacity for islet growth, the metabolic load is an important influence. This is shown by the use of pair-fed controls and by the authors' critical discussion of the mechanisms by which pituitary extracts may act. Since the diabetic cannot respond to an ample food intake with the normal secretion of insulin, this modern study confirms the value of dietary restriction in diabetes mellitus. Finally, these methods have been applied to man. Thus, Ogilvie[1] and Wrenshall[2] have found that both the islet volume and the extractable insulin of the pancreas *per unit of body weight* decrease with age. It is more true than facetious to say that obesity is a weighty predisposing factor to diabetes, and one may suppose that this is in part due to the limited ability of the islets of the adult to grow adequately in response to this metabolic demand. In any case the information gained by these studies is not only of value at the moment but is an incentive to further clinical application of methods developed in the laboratory.

FRANCIS D. W. LUKENS, M.D.

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CLAUDE BERNARD, 1813-1878

J. M. D. Olmsted, Ph.D., D.Sc., BERKELEY, CALIFORNIA

A PIONEER IN THE STUDY OF CARBOHYDRATE METABOLISM

The old farmhouse where Claude Bernard first saw the light of day in 1813 stands on the brow of the hill overlooking the little village of St. Julien, some twenty kilometers from the busy industrial city of Lyons, France. The house today is surrounded by row upon row of grapevines, as it was at the time of his birth, but there has been affixed to it a plaque showing that it is now a national shrine in which are preserved the relics of the country boy who became the most illustrious physiologist that France, if not the world, has produced.

After attending nearby schools, Bernard was apprenticed in his late teens to an apothecary in Lyons; an occupation which brought him into contact with one aspect of medical science, the compounding of drugs. However, attending the theatre proved a more enjoyable occupation, so, caught up in the rising tide of the romantic movement, he tried his own hand at writing a play. The local success of this first effort spurred him on to write a second, which he thought was so good that it should bring him recognition in the capital. Once in Paris, however, his literary hopes were dashed and he was persuaded to enter medicine; a field not too unrelated to his previous training. Toward the end of his medical course, his skill at dissection attracted the notice of François Magendie, the pioneer exponent of experimental physiology, and, being taken on as this professor's laboratory assistant at the Collège de France, in 1841 his life's course was fixed.

Bernard never practiced medicine but devoted his whole time and energy to physiological investigations. Although he was employed in Magendie's laboratory, for his own original investigations he had to maintain and operate on his animals for several years in various out of the way corners in the maze of the Latin Quarter. His skill in dissection influenced these experiments, and certain of his earliest published papers, although directed toward the general question of digestion and the transformation of the products of digestion into the substance of the living body, actually dealt with the anatomical relations of the tiny chorda tympani nerve in the ear, and the spinal accessory nerve. He really got into his stride when he showed, in 1846, that the pancreas, in addition to secreting digestive agents which act on proteins and carbohydrates, also secretes a fat-splitting enzyme. It was in the course of these experiments that he attempted to depancreatize dogs, and produced in several animals symptoms which today would be recognized as indicative of the diabetic condition; namely, extreme emaciation in spite of a voracious appetite, and death by wasting away. Had he followed up this lead, it is not impossible that he might have anticipated the discovery of insulin by three quarters of a century.

Address communications to Dr. Olmsted, Department of Physiology, University of California, Berkeley, Calif.

FUNCTIONS OF THE LIVER

His next discovery, however, did lay the foundations for our understanding of the physiological mechanisms which are disturbed in the diabetic condition, and most medical historians would say that Bernard's discovery of the glycogenic functions of the liver is the greatest of all his achievements.

The prevailing theory at that time was that only plants were capable of synthesizing materials; it was thought that animal metabolism consisted merely in breaking down substances originally supplied by plants. Bernard demonstrated that in the liver of a dog which had been fed exclusively on lean meat (and therefore on food from an animal source), he had discovered a starch-like substance, which although itself not a true sugar, could readily be transformed into glucose and appeared in the blood as such. To this compound he gave the name gycogen; that is, sugar-forming. He then found that in the normal animal, blood leaving the

liver is richer in sugar than blood entering it. He argued that must mean that the liver could release its product directly into the blood stream ("internal secretion" as he termed it), in contrast to the well-known action of glands which release their products to the exterior through a duct. This idea was the origin of our present day endocrinology. Furthermore, he showed by his now famous piqûre experiment that the nervous system was involved in these reactions. This experiment consisted in wounding a small area in the floor of the fourth ventricle of the brain—even a pinprick would suffice—with the result that so great an amount of glucose was released into the blood stream that it appeared almost at once in the urine in considerable quantity. This condition, he described as "artificial diabetes."

CONSTANT EXPERIMENTATION

It must not be imagined that the story, told here in merest outline, of the discovery of these basic concepts of normal carbohydrate metabolism, a knowledge of which seems to us so necessary for an understanding of what may go wrong in the diseased state, was worked out in a short period of time. It took Bernard some fourteen years of constant experimentation before he arrived, in 1857, at the point of isolating the chemical compound in the liver which he had predicated long before. He read no foreign language and consequently did not know that a German investigator, Hensen, had anticipated him by nearly a year in reporting the successful isolation of glycogen. To this writer, this does not detract from the admiration due Claude Bernard for his steadiness of purpose, his gradual unfolding of one essential physiological fact after another until the essentials of an account of the glycogenic function of the liver were rounded out, and it only remained for future investigators to fill in the details. The completeness of this series of discoveries is unique in the history of physiology.

From 1843 to the end of his life (he died in 1878 at the age of 65) he retained an ardent interest in the subject of diabetes. He had succeeded Magendie as Professor of Medicine at the Collège de France in 1855, and in the very year before his death, Bernard published a series of lectures which he had delivered there entitled, "Lectures on diabetes and animal glycogenesis." In this volume of his late maturity, we find a clear statement of his attitude toward what in his most famous book, written twelve years earlier, he had called "experimental medicine," for he considered that so-called "morbid symptoms" are in reality "physiological phenomena, more or less exaggerated," and are therefore suitable material for experimentation. He shows the relation of sugar in the urine to sugar in the blood, traces the sugar back in the deposit of glycogen in the liver, and comments on the relation of different kinds of foods to the symptoms of diabetes. These lectures afford an excellent picture of the ideas about this disease current in the 1870's, and show, as well, Bernard's methods in attacking medical problems.

VASOMOTOR NERVES

His third great discovery was the action of vasomotor nerves. He was able to demonstrate that certain nerves when stimulated cause vasoconstriction; others, vasodilation. The caliber of our blood vessels is therefore under nervous control, and is not merely an expression of the amount of blood forced through them. This means that blood flow through a given part of the body is dependent on, and related to, functions in other parts, and is an illustration of his celebrated doctrine of the constancy of the "internal environment," that is, that state of dynamic equilibrium which is life itself. Although changes are constantly going on in the living body, these changes can proceed only so far before counteracting reactions set in; otherwise, death ensues.

A reflection of Bernard's early occupation as a pharmacist's apprentice may be seen early in his career as a physiologist, though it is much more probable that the immediate stimulus to his investigation of the action of certain drugs and poisons was the work which his master, Magendie, had done on strychnine quite early in the century. This drug, and samples of plants containing it, had been brought from Java to France by explorers, and Magendie was so fascinated by the violent death following its administration, that he began a long series of investigations to show how it was absorbed into the body, and its site of action. Bernard, in 1844, was presented with some South American arrows whose tips were coated with curare. To him, the astonishing feature about curare poisoning was the quietness with which the animals died, a striking contrast to the effects of Magendie's strychnine. Bernard was able to show that the curarized animal dies of asphyxiation; and because of the paralysis of all skeletal muscles, including those used in respiration, the death is a quiet one. His location of the site of the action of the drug is a classic example of the syllogistic reasoning followed by all experimenters when planning their experiments. He argued that the curare might attack the motor nerve; the muscle itself; or possibly

the junction between nerve and muscle. By a simple, ingenious experiment he showed that in a curarized frog, motor nerves can still conduct and skeletal muscles still contract if stimulated directly, therefore the drug must exert its paralysing effect at the myoneural junction. No one would have guessed that a century after Bernard had satisfied his curiosity in solving this apparently academic question, his answer would prove to be of direct service to the clinician.

This brief summary of Bernard's contributions to physiology far from exhausts the list of his discoveries. It has been given to few experimenters to enrich their chosen science with so many important discoveries and fruitful ideas as he did. Although Bernard's work stopped three quarters of a century ago, a present day scientist, no matter what his field, can read with profit "The Introduction to Experimental Medicine." This is Bernard's own analysis of how his mind worked in making his discoveries, and won for him a seat among the Forty Immortals of the French Academy.

BOOK REVIEW

CLAUDE BERNARD AND THE EXPERIMENTAL METHOD IN MEDICINE, by J. M. D. Olmsted and E. Harris Olmsted, $4.00, Pp. 277, New York, Henry Schuman. 1952

Doctor and Mrs. Olmsted have collaborated in the production of this fascinating life story of the man they consider to be one of the founders of experimental medicine. It furnishes adequate evidence to justify the esteem and reverence of the authors in giving him this title.

"Why is the name of Claude Bernard associated with the experimental method as applied to medicine? The method is as old as science itself, and its application to medicine, although long delayed, was made through physiology two centuries before Bernard's time by William Harvey in England. In France, the experimental method was reinstated for medicine at the beginning of the nineteenth century by François Magendie, under whom Bernard was proud to have served his apprenticeship as a physiologist. Many of Bernard's contemporaries, especially in Germany, were using the experimental procedure with increasing success.

"In the first place, the sum of Bernard's achievements finally silenced skepticism about the power of experiment to draw from nature the secrets of the living organism. His work closed a period in the history of medicine. Considered singly, none of these discoveries was of the sort which transforms the whole scene overnight. Yet each brought to light some fundamental truth of organic function; and the whole of his accomplishment in the twenty years of his greatest activity, 1839 to 1859, did transform the scene and make him the foremost physiologist of his time.

"In the second place, after his most intensive period of work, Bernard paused to harvest his experience in another way. He composed a description of the experimental method as applied to physiology, and illustrated it by his own researches . . . ." This reference to his famous book: "Introduction to the Study of Experimental Medicine" gives an indication of its great influence, which has continued to recent times.

The article on Claude Bernard in this issue of DIABETES gives brief information regarding his life and points out specifically his achievements in relation to diabetes and associated physiological problems. The book gives interesting details concerning his early days as a French country boy and as a medical student in Paris; it describes his distinguished scientific career throughout his long adult life.

The authors are well qualified to write this book both from the standpoint of an understanding of physiology and interpretative biography. Doctor Olmsted was educated at Middlebury College and Harvard University and went to Oxford as a Rhodes scholar. He taught physiology at Harvard, Johns Hopkins, and the University of Toronto, and at present is Professor of Physiology at the University of California. Mrs. Olmsted holds degrees from Oxford University in England and the University of Toronto. She has been lecturer of classics at University College, University of Toronto. The book can be recommended not only to physicians and students of the biological sciences, but also to the general reader.

REPORT OF THE COMMITTEE ON DETECTION AND EDUCATION

During Diabetes Week, November 16-22, the fifth annual Diabetes Detection Drive was renewed with a nationwide screening effort by over 800 local committees. Since the statistics of the activity are not complete at the present time, this report must, of necessity, be in the nature of a commentary on the program as a whole.

In 1948, the American Diabetes Association started the detection and education program for the purpose of alerting the medical profession and the public to the need for early diagnosis and proper management of this ailment. Inaugurated under the able chairmanship of Dr. Howard F. Root, the annual program has increased in scope and effectiveness in the years that followed. Diabetes Week has been set aside for the recognition of this work and it has been endorsed by many national and professional organizations. There has been a steady and impressive growth of educational material on our program appearing in professional and lay publications and being broadcast through radio and television channels.

Organizationally, there has been excellent cooperative action by our 31 affiliate associations and by an additional 800 committees of State and County Medical Societies supported by educational, civic, industrial, labor and service groups throughout the country. For details, I can refer you to the progressive reports issued by the national office of the Association. (See DIABETES 2: 81-82, Jan.-Feb. 1953)

When we started this professional and public educational program, we outlined certain basic concepts to guide our organization. First, it was agreed that our approach to a chronic condition like diabetes must be along the lines of preventive medicine. The disabling effects of diabetes could often be prevented, if discovered early and proper management was instituted promptly.

This approach then led to the need for medical technics to discover early diabetes or metabolic tendencies toward that condition, and an organizational form for bringing such detection apparatus to the public, so that large numbers of persons could use it quickly and effectively. This, in turn, led to nationwide community organization, with extensive public education and participation.

It has been axiomatic with the American Diabetes Association that it is the responsibility of the medical profession to discover and diagnose diabetes as early as possible. This concept has been adopted by many other groups which have developed preventive medical programs. But while it is the primary responsibility of the physicians of America to undertake detection and prevention programs, it becomes necessary for their success that a network of community organization be set up, under the leadership of the medical profession, which can bring this program to groups and individuals in all walks of life. Indeed, from our experience, as well as that of others conducting similar prevention programs, it is evident that the better the community organization the more effective the detection program.

Planning at the community level, the Association has secured the widespread cooperation of state and county medical societies in carrying out the screening program and the education of the public to the necessity of prompt detection of diabetes. The thirty-one affiliates of the Association have done yeoman work in organizing Diabetes Detection Drives in their communities. Many have displayed initiative and originality in amplifying plans of the National Committee, and have contributed new technics and educational presentations that have added to the general effectiveness of every section of our organization.

The acceptance of our detection and education program is evidenced by the ever increasing growth in numbers of medical groups participating in the nationwide search for the unknown diabetic. They now num-

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The above report was presented at the interim meeting of the Council of the American Diabetes Association, January 17-18, 1953. It was accepted with commendation for Dr. Reed and his committee.

Dr. Reed was reappointed chairman of the committee for the current year, and will proceed with plans for the sixth annual Diabetes Detection Drive.

ber over 800, as I mentioned before. There is also no question of the growing public awareness of the need for early diabetes detection. The impressive newspaper and radio space and time donated to our Diabetes Week activities is a further confirmation of civic appreciation for our efforts.

It is the opinion of the Committee that this program of detection and education has proved its worth and should be continued and expanded. Careful examination should be made of all its phases with a view to improving them and increasing the number of individuals screened. The problem of follow-up studies should be emphasized; where they have been inaugurated they have been most revealing and of great value from a medical point of view.

Any shortcomings of this detection and education program seem to be those of execution, rather than of principle or planning. The organization of so large a public as ours by voluntary means is not easy, and although our community facilities for testing have grown over the years, there is still vast room for expanding this accommodation. The acceptance of our publicity, both professional and public, has been gratifying. Records and displays at the National Office are witness to that.

Increased efficiency in the work of the Committees on Diabetes, conscientious record-keeping and prompt reporting, as well as intelligent follow-up studies of individuals tested will improve the effectiveness of our work. These have improved over the years, and I have no doubt but that they will continue to improve until our highest expectations have been reached.

One phase of this work, which is an inevitable concurrent, is education, both to the laity and the profession, which conforms to a basic concept of this Association. A distinct effort should, and is, being made to broaden this very important aspect of the program.

Each year we are able to detect and advise many unknown diabetics so that they are able to take measures which will prevent their developing disabling future complications. As we see this figure growing, we can feel assured that the American Diabetes Association and its cooperating groups are performing a real service to the American people.

JOHN A. REED, M.D., *Chairman,*
Committee on Detection and Education

The First Postgraduate Course in Diabetes Successfully Completed

The first Postgraduate Course in diabetes and basic metabolic problems conducted by the American Diabetes Association, under the direction of Charles H. Best, M.D., Director of the Banting and Best Department of Medical Research of the University of Toronto, was held successfully at the University of Toronto on January 19, 20, and 21, 1953.

The organization and the presentation of the Postgraduate Course, under the chairmanship of Edward L. Bortz, M.D., and the Committee on Postgraduate Education, was commented on universally, with special appreciation of the work of the Course's Clinical Director, Ray F. Farquharson, M.B., Professor of Medicine of the University of Toronto, and Associate Clinical Director Andrew L. Chute, M.D., Professor of Pediatrics at the University of Toronto, who placed the facilities and the conveniences of the Hospital for Sick Children at the disposal of all who attended the Course. The new hospital's excellently designed and comfortable lecture theatre provided an ideal setting for the talks and discussions and the facilities of its staff cafeteria were available throughout the day for luncheon and other refreshments.

REGISTRANTS REPORT

As to the Course itself, which is now history, the best report on it can be found among the three-page questionnaires which were distributed to the registrants for their comment on the value of each lecture and discussion as well as their estimate of the manner of its presentation. Although signature to this questionnaire was optional, reports of those attending were uniformly favorable. Here are some quotations from the registrants' remarks:

"I have attended numerous postgraduate courses and

I feel that this course was as beneficial, as well organized, and that the caliber of teachers was as high as any I have attended."

"The entire course was well worth while. The program was excellent, showed thoughtful planning, and was presented on a well-timed schedule. . . . Presentations were usually concise, bearing well on salient points, well organized."

"I feel that the course is excellent and very worth while to practcing physicians. Especially noteworthy were the round-table discussions and the courtesy and friendliness of the speakers between and after classes."

"Very well planned. Very well carried out. Very thoughtful of our personal individual comfort. A fine meeting."

"An excellent course, full of meat. Impossible to digest all of it. Will be necessary to attend future courses to profit to the full from this one. Many excellent features of great value to the General Practitioner as well as the Internist Specialist. It would have been perfect if we had been supplied with copies of those papers, the contents of which could have been put to practical use."

Many of the papers given at the Course will be published in future issues of DIABETES.

Physicians from 24 of the United States and the District of Columbia, and Canadian physicians from three provinces, comprised the 176 registrants. Due to lack of facilities, 78 applicants for the Course had to be declined and many inquirers had to be advised that the Course was oversubscribed. All Association members who applied were accepted.

We are pleased to report that we received many applications for membership in the American Diabetes Association as a result of the Course, as well as a substantial number of new subscriptions to DIABETES.

SOCIAL EVENTS

In addition to the three daily sessions of lectures and round-table discussions which were enthusiastically and attentively attended, the social facilities of Toronto were placed at the disposal of the registrants. Excellent symphony concerts, ballets, and theatrical attractions, as well as hockey, football and other sports were listed daily.

The dinner on Monday evening, January 19, was attended by 225 persons. The speakers' table was graced by Lady Banting; Mrs. Frederick W. W. Hipwell, whose late husband was a Councilor of the Association and a cousin of Sir Frederick Banting; Doctors Almon Fletcher and W. R. Campbell, who were the first to use insulin clinically; Emeritus Professor Duncan Graham of the University of Toronto and Mrs. Graham; Dean J. A. MacFarlane of the Medical School of the University of Toronto and Mrs. MacFarlane; Professor and Mrs. Charles H. Best; Dr. Frank N. Allan, who was toastmaster, and Mrs. Allan; Dr. R. F. Farquharson, and Mrs. Farquharson; Dr. A. L. Chute, and Mrs. Chute; Dr. Edward L. Bortz.

The high point of this distinguished social event was the showing by Dr. Charles H. Best of slides taken during several of his recent world-wide trips—a travelogue of fascinating scientific and historical interest.

ASSOCIATION NEWS

THIRTEENTH ANNUAL MEETING, MAY 30-31, 1953
HOTEL COMMODORE, NEW YORK CITY

The forthcoming Annual Meeting promises to be the largest one ever held by the Association and attendance at the Scientific Sessions on Saturday afternoon, May 30, and all day Sunday, May 31, 1953 is expected to exceed previous records.

A large number of rooms for individual accommodations has been set aside at the Hotel Commodore, but in view of heavy registrations, member are urged to make their reservations early. Prepaid reservation cards were sent to the membership early in February. If the card has been mislaid, however, members may secure an additional one from the National Office. The hotel will accept reservations through the Annual Session of the American Medical Association, June 1-5.

SCIENTIFIC SESSIONS

Doctor Henry B. Mulholland, Chairman of the Committee on Scientific Programs, has announced that a greater number of abstracts of papers for presentation at the Scientific Sessions has been received this year than ever before.

Final selection of the papers is in process and the program is scheduled to be sent to the membership in April, as well as being printed in the next (May-June) issue of DIABETES.

Two highly interesting and informative panels have already been arranged for the Sunday Sessions. They are:

"Clinical Use of Insulin"—Arthur R. Colwell, M.D., Moderator; Garfield G. Duncan, M.D., Robert L. Jackson, M.D., Alexander Marble, M.D., Franklin B. Peck, M.D., and Donald S. Searle, M.D.

"What It Means to Live with Diabetes"—Frederick W. Williams, M.D., Moderator; Peter H. Forsham, M.D., Ingebord K. Hinck, M.D., Norman H. Jolliffe, M.D., Leon S. Smelo, M.D., and Randall G. Sprague, M.D.

Those planning to attend the Meeting are requested to send questions intended for the above panels to the National Office in advance.

As previously announced, there will be a joint meeting of The Endocrine Society and the American Diabetes Association on Saturday afternoon, May 30, at the latter's headquarters in the Hotel Commodore. Shields Warren, M.D., will give the Banting Memorial Lecture, entitled "Interpretation of Diabetes in the Light of Its Pathology", at that joint session.

BANQUET

Over 400 members have already indicated their intention to attend the Banquet on Saturday evening, May 30, at 7:15 o'clock. An innovation this year will be a social hour, beginning at 6:30 o'clock, which will precede the Banquet. In accordance with the membership announcement of February 5, dinner tickets are available at $6.75 each and may be secured from the National Office prior to May 20. The social hour is by individual subscription. Members, their families and friends are cordially invited to attend both functions.

Shields Warren, M.D., will be awarded the Banting Medal at the Banquet. In addition, Banting Medals will be given to Doctors Walter R. Campbell and Almon Fletcher of Toronto, Canada, who were the first users of insulin clinically and contributed so much to its early clinical development. Presentation of the Medals to Doctors Campbell and Fletcher will be made by Doctor Charles H. Best.

Citations will be conferred on outstanding laymen and members of other professions who have rendered distinguished service to the Association.

SCIENTIFIC EXHIBITS

The Association has the following excellent scientific exhibits available for current use: "Diabetes Detection by the Physician" and "Vascular Complications of Diabetes".

The latter was shown at the Interim Meeting of the American Medical Association in Denver, Colorado, December 2-5, 1952. This exhibit is scheduled for display at the meetings of the Chicago Medical Society, March 3-6, 1953, and the American Academy of General Practice, St. Louis, March 23-26, 1953. It will also be shown at the Annual Session of the American Medical Association, June 1-5, 1953, at Grand Central Palace, New York City.

"Diabetes Detection by the Physician" was shown at the First Congress of the International Diabetes Federation, July 7-12, 1952, Leyden, The Netherlands, and at many other meetings.

DEADLINE FOR PAPERS ON DIABETES BY MEDICAL STUDENTS AND INTERNS

Members and subscribers are urged to remind medical students and interns at their schools and hospitals of the closing date of this competition for a prize of $250.00, made possible by the St. Louis Diabetes Association. *April 1, 1953,* is the deadline on which manuscripts for the above may be submitted.

Papers should be sent to the Editorial Offices of DIABETES: The Journal of the American Diabetes Association, 11 West 42nd Street, New York 36, New York.

NETWORK RADIO PROGRAM ON DIABETES

On Tuesday, March 3, at 9:05 p.m., a 25-minute radio program on diabetes was carried over the Mutual Broadcasting System as part of the weekly serial, entitled "The Search That Never Ends", sponsored by the Institute of Life Insurance. The program was developed in cooperation with our Association.

CORRECTION

Four papers composing a symposium on lipoproteins in relation to diabetes were published in the Nov.-Dec., 1952, issue of this Journal, accompanied by discussions which followed their presentation at the Annual Meeting of the American Diabetes Association, Chicago, Illinois, June 8, 1952.

These discussions were printed following the first of these papers. They should have appeared at the end of the fourth article, since the discussions were related to all four papers, not to just a single paper in the series.

PERSONAL

The following members of the Association participated in a course on "Pathology and Pathologic Physiology in Internal Medicine" conducted by the American College of Physicians, February 16-22, 1953, at Cleveland, Ohio: E. Perry McCullagh, M.D., Max Miller, M.D., Robert W. Schneider, M.D., Penn G. Skillern, M.D.

A "Panel Discussion on Diabetes" is scheduled for 9 o'clock of the evening of March 17, 1953, during the Second Midwinter Seminar of The Medical Society of the District of Columbia. Russell M. Wilder, M.D., Director of the National Institute of Arthritis and Metabolic Diseases, will be Moderator, and Louis K. Alpert, M.D., of Washington will be among those on the panel.

The 25th annual letter of the Central Society for Clinical Research announces that Jerome W. Conn, M.D., was elected Vice President for 1953 and Randall G. Sprague, M.D., is on the Society's Board of Councilors.

NEW MEMBERS

Beginning with this issue of DIABETES, the names of members newly elected to the Association will be published as often as practicable.

Physicians elected to Active Membership since January 1 of this year are:

ELADIO A. ARMENGOL
Habana, Cuba

SHEPARD G. ARONSON
New York City

HARRY W. BAIN
Toronto, Ontario, Canada

FRANKLIN A. BRYAN
Fort Wayne, Indiana

JOSEPH C. CALITRI
Lawrence, Massachusetts

JOHN W. CHRISS
Rochester, Minnesota

WM. T. W. CLARKE
Toronto, Ontario, Canada

SIDNEY S. LAZARUS
Brooklyn, New York

JOHN J. B. LIGHT
Lebanon, Pennsylvania

EDWARD O. LUKASEK
Sparta, Wisconsin

JAMES J. MCGINNIS
San Francisco, California

ROY J. PHILIPP
Buffalo, New York

IRWIN J. PINCUS
Philadelphia, Pennsylvania

ARTHUR B. RICHTER
Indianapolis, Indiana

J. HAL DORAN *Indianapolis, Indiana*	WILLOUGHBY ROTHROCK *Washington, D. C.*
JOSEPH R. EVANS *Salt Lake City, Utah*	DAVID W. SINTON *Iowa City, Iowa*
ROBERT C. GREEN, JR. *Rochester, Minnesota*	JAMES M. SKELTON *Houston, Texas*
HECTOR E. GUAITA *Buenos Aires, Argentina*	EUCLID M. SMITH *Hot Springs, Arkansas*
HOWARD M. HACKEDORN *Seattle, Washington*	SAMUEL SPIRO *Far Rockaway, New York*
ATLEE B. HENDRICKS *Davenport, Iowa*	JOHN F. STAPLETON *Rockville, Maryland*
LAWRENCE E. HINKLE, JR. *New York City*	DELMONT M. ULRICH *Seattle, Washington*
CONRADO B. ICASIANO *Kamias, Quezon City, P. I.*	HIRAM VAZQUEZ-MILAN *Santurce, Puerto Rico*
IRVING IMBER *Reading, Pennsylvania*	HARRY F. WEISBERG *Chicago, Illinois*
GLENN WARD IRWIN *Indianapolis, Indiana*	WARREN F. WILHELM *Kansas City, Missouri*
BYRL J. KENNEDY *Minneapolis, Minnesota*	WALTER H. WILSON *Raleigh, North Carolina*

Information and application blanks relative to Active or Associate Membership in the Association may be secured from the National Office.

OBITUARIES

Charles Robert Reiners, M.D., of Huntington, Pennsylvania, a member of the American Diabetes Association since 1945, died on May 9, 1952 at the age of 61. He received his doctorate from the University of Pennsylvania School of Medicine in 1913 and was associated with the Medical Service Pathologoical Laboratory of the J. C. Blair Memorial Hospital, Huntington, Pennsylvania. He was a member of the American Society of Clinical Pathologists.

JOSEPH EMMETT HIRSH, M.D., a member of the American Diabetes Association, died of a heart attack at Baton Rouge, La., on September 27, 1952, at the age of 54 years. Born in Shenandoah, Pa., he received his B.S. in 1918 from the University of Alabama and the degree of M.D. from the University of Pennsylvania in 1922.

Doctor Hirsh interned at the Philadelphia General Hospital from 1922 to 1924. He then went into private practice in Birmingham, Alabama; interrupting it to go to Vienna for a period of postgraduate study in 1926.

For many years he was a member of the staffs of Hillman Hospital,, Jefferson Hospital, St. Vincent's Hospital, and South Highlands Infirmary, all of them in Birmingham. He was certified by the American Board of Internal Medicine and was a Fellow of the American College of Physicians among many other organizations.

Doctor Hirsh was Professor of Clinical Medicine at the University of Alabama.

WALTER H. NADLER, M.D., a member of the American Diabetes Association, died in Chicago on September 13, 1952 at the age of 63 years. Born in Peru, Illinois, he received his M.D. from the Northwestern University Medical School and was Associate Professor of Medicine at Northwestern for many years. In 1944, he was president of the staff at Passavant Memorial Hospital, and from 1943 to 1950 chief of medical service.

He was a member of the attending staff in Contagious Diseases at Cook County Hospital and later became a consultant on the medical service at Hines Veterans Hospital where he served from 1928 to 1952.

Doctor Nadler was a member of the Institute of Medicine of Chicago and the Central Society for Clinical Research among many other organizations.